



2011

TORONTO NOTES

COMPREHENSIVE MEDICAL REFERENCE & REVIEW FOR MCCQE I & USMLE II



Editors-in-Chief:
Yingming Amy Chen & Christopher Tran

THE TORONTO NOTES 2011

Comprehensive medical reference and review for the
Medical Council of Canada Qualifying Exam Part 1 and the
United States Medical Licensing Exam Step 2

27th Edition

Editors-in-Chief:

Yingming Amy Chen and Christopher Tran

*Wherever the art of medicine is loved,
there is also a love of humanity.*

– Hippocrates



Toronto Notes for Medical Students, Inc.
Toronto, Ontario, Canada

Twenty-seventh Edition

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Toronto, Ontario, Canada.

Typeset and production by Type & Graphics Inc.

ISBN 978-0-9809397-4-3 (27th ed.)

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Cover design: John Sauvé and Stephanie VandenBerg

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The editors of this edition have taken every effort to ensure that the information contained herein is accurate and conforms to the standards accepted at the time of publication. However, due to the constantly changing nature of the medical sciences and the possibility of human error, the reader is encouraged to exercise individual clinical judgement and consult with other sources of information that may become available with continuing research. The authors, editors, and publisher are not responsible for errors or omissions or for any consequences from application of the information in this textbook, atlas, or software and make no warranty, expressed or implied, with respect to the currency, completeness, or accuracy of the contents of the publication. In particular, the reader is advised to check the manufacturer's insert of all pharmacologic products before administration.

Library of Congress Cataloging-in-Publication Data is available upon request

To the contributors of past, present and future editions,

and

*To the families, friends, and loved ones of those who participated
in the Toronto Notes 2011 production – your support and
understanding were invaluable in the success of this project!*

Thank You!

The Toronto Notes is dedicated to helping fund many charitable endeavours and medical student initiatives at the University of Toronto's Faculty of Medicine. Programs that have received Toronto Notes funding include:

Community Affairs Projects

- Saturday Program for Inner City High School and Grade 8 students
- St. Felix Mentorship Program for Inner City children
- Parkdale Mentorship Program for Grade 10-12 students
- WoodGreen Community Centre
- Let's Talk Science
- Growing Up Healthy

Annual Faculty Showcase Events

- Daffydil, in support of the Canadian Cancer Society
- Earthtones Benefit Concert
- Clerkship Luncheon

Medical School Clubs

- Books with Wings
- Women in Medicine
- University of Toronto International Health Program
- Complementary and Alternative Medicine
- Peer Support for Students
- History of Medicine Society
- Faculty of Medicine Yearbook

Graduating Class

- Bruce Tovee Lecture Series
- Convocation and Ceremonies
- Scholarships and Bursaries

NOTE:

Many of you have wondered about the *Toronto Notes* logo, which is based on the rod of Asclepius, the Greek god of medicine. The rod of Asclepius consists of a single serpent entwined around a staff. This icon symbolizes both rebirth, by way of a snake shedding its skin, and also authority, by way of the staff.

In ancient Greek mythology, Asclepius was the son of Apollo and a skilled practitioner of medicine who learned the medical arts from the centaur Chiron. Asclepius' healing abilities were so great that he was said to be able to bring back people from the dead. These powers displeased the gods, who punished Asclepius by placing him in the sky as the constellation Orphiuchus.

The rod of Asclepius is at times confused with the caduceus, or wand, of Hermes, a staff entwined with two serpents and often depicted with wings. The caduceus is often used as a symbol of medicine or medical professionals, but there is little historical basis for this symbolism.

As you may have guessed, our logo uses the rod of Asclepius that is modified to also resemble the CN Tower – our way of recognizing the university and community in which we have been privileged to learn the art and science of medicine.

Thomas O'Brien, HBSc, MD
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Preface – From the Editors

Dear Readers,

Toronto Notes is a concise and comprehensive medical review revised annually by the University of Toronto graduating medical class under the guidance of leading experts within the Faculty of Medicine. This reference text started as a compilation of notes written by and shared among University of Toronto students to study for their medical licensing exams. After 27 years, it has become a reputable study guide used by medical students across Canada and around the world. This transformation could not have happened without the dedication of students who ensure that each edition contains the latest evidence-based information on 29 subspecialties of Medicine. This year has been no different: over 100 staff worked tirelessly to complete this edition.

Since its inception, *Toronto Notes* has been a non-profit organization where revenue is used to fund University of Toronto medical student initiatives including community outreach, international health projects, charitable performances, and graduating class scholarships and bursaries. On behalf of the *Toronto Notes* production team, we would like to thank the support from thousands of medical students around the world by purchasing our book.

The 27th edition of *Toronto Notes* offers exciting new changes to further enhance your exam preparation. We have included over 20 new original medical illustrations, updated our online colour atlas with new images and annotations, and revised our evidence-based medicine reviews. We also have a new learning module: the Approach to Ultrasound in the Emergency Department, created to help medical students understand the basics of ultrasound imaging in trauma and other emergencies. In addition, we have included over 50 Objective Structured Clinical Examination (OSCE) scenarios with history and physical exam checklists for practice purposes that can be found online. We have also separated our popular *Clinical Handbook* into four pocket reference guides for easy portability.

As readers, we appreciate your feedback. This year, we have spent considerable time improving the scientific and writing accuracy of our publications. Many of those changes originated from your comments submitted online on our website. Having travelled across the country for electives, we appreciate how so many medical students value *Toronto Notes* for studying during clinical rotations and exam preparation. We therefore understand the trust placed in our publication and realize our crucial task in upholding the accuracy of our content.

Thank you very much for purchasing the 2011 edition of *Toronto Notes*. We hope it will serve you well in all of your future medical endeavours.

Sincerely,



Yingming Amy Chen

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Christopher Tran

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Feedback and Errata

We are constantly trying to improve the Toronto Notes and welcome your feedback. If you have found an error in this edition please do not hesitate to contact us. As well, we look forward to receiving any comments regarding any component of the Toronto Notes package and website.

Please send your feedback to: feedback@torontonotes.ca

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This book has been designed to remain as one book or to be taken apart into smaller booklets. Identify the beginning and end of a particular section, then carefully bend the pages along the perforated line next to the spine of the book. Then tear the pages out along the perforation.

The layout of *Toronto Notes 2011* allows easy identification of important information. These items are indicated by icons interspersed throughout the text:

Icon	Significance
	The 'key' icon, found next to headings in the text, identifies key objectives and causal conditions as defined by the Medical Council of Canada or the National Board of Medical Examiners USA. If it appears beside a 'black-bar' title, all subsequent subheadings should be considered key topics.
	The 'pearl' icon, found in the sidebar, identifies concise, important information which will aid in the diagnosis and/or management of conditions discussed in the accompanying text.
	The 'light bulb' icon indicates helpful mnemonic devices and other memory aids.
	The 'flag' icon indicates information or findings that require urgent management or specialist referral.
	The 'camera' icon indicates topics that correspond with images found in the Colour Photo Atlas available online.
	The 'X-ray' icon indicates topics that correspond to information or images contained within the Radiology Atlas located online.
	The 'computer' icon indicates topics that correspond with electronic resources such as Functional Neuroanatomy™ or ECG Made Simple™ located online.

Chapter Divisions

To aid in studying and finding relevant material quickly, each chapter is organized in the following general framework:

Basic Anatomy/Physiology Review

- features the high-yield, salient background information students are often assumed to have remembered from their early medical school education

Common Differential Diagnoses

- aims to outline a clinically useful framework to tackle the common presentations and problems faced in the area of expertise

Diagnoses

- the bulk of the book
- etiology, epidemiology, pathophysiology, clinical features, investigations, management, complications, and prognosis

Common Medications

- a quick reference section for review of medications commonly prescribed

Ethical, Legal and Organizational Aspects of Medicine

Trevor Arnason and Shuo Chen, chapter editors
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Further information on these topics can be found in the *Objectives of the Considerations of the Legal, Ethical and Organizational Aspects of the Practice of Medicine (CLEO)* – which can be downloaded free of charge from the Medical Council of Canada website at www.mcc.ca/pdf/cleo.pdf

Legal Matters

The Doctor-Patient Relationship under the Law



N.B.: Canadian law applicable to medical practice varies between jurisdictions and changes over time.

- Criminal law is nationwide, but non-criminal (civil) law varies between provinces.
- This section is meant to serve only as a guide; students and physicians should ensure that their practices conform to local and current laws.



Fiduciary duty: obligation to act in the patient's best interests

- laws which regulate doctor-patient relationship function to protect patients
- derived from three sources: 1) **common law** (in Quebec, the *Civil Code of Quebec*), 2) **statutes** and 3) **the Constitution**
- **common law:** body of legal rules and principles derived from judges' decisions that forms the basis of the Anglo-Canadian legal system, includes:
 - *tort law* that allows patients to recover damages for wrongful acts committed against them. The most important are 1) *negligence* (see *Negligence and Liability*, ELOAM6) and 2) *battery* (the application of force to a person's body without their consent)
 - the doctor-patient relationship is a contract of *contractual rights and obligations* that if breached may result in the award of damages
 - a doctor also has a *fiduciary* duty to their patient
- **statutes** are laws passed by provincial legislatures and the federal parliament, for example:
 - in Ontario, the *Health Care Consent Act* regulates consent to treatment (see *Consent under the Law*, ELOAM2)
 - the *Personal Health Information Protection Act* regulates the collection, use and disclosure of health records (see *Privacy of Medical Records*, ELOAM5)
- **the Constitution** is the supreme law of Canada; all other laws must be consistent with it
 - the *Canadian Charter of Rights and Freedoms* guarantees the rights of life, liberty, security of the person, and equality under the law (among others)
 - these rights are subject only to such reasonable limits as can be demonstrably justified in a free and democratic society



Consent under the Law

- consent of the patient must be obtained before any medical intervention is provided. Consent can be:
 - oral or written, although written is usually preferred
 - implied (e.g. a patient holding out their arm for an immunization) or expressed
- consent is an ongoing process and can be withdrawn or changed after it is given
- *Health Care Consent Act* covers consent to treatment, admission to a facility, and personal assistance services (e.g. home care)

Exceptions to Consent

1. Emergencies

- treatment can be provided without consent where a patient is experiencing severe suffering, OR where a delay in treatment would lead to serious harm or death AND consent cannot be obtained from the patient or their substitute decision maker (SDM)
- emergency treatment should not violate a prior expressed wish of the patient (e.g. a signed Jehovah's Witness card)
- if patient incapable, MD must document reasons for incapacity and why situation is emergent
- if a SDM is not available, MD can treat without consent until the SDM is available or the situation is no longer emergent

2. Legislation

- Mental Health legislation allows for:
 - ♦ the detention of patients without their consent (see *Consent*, ELOAM8)
 - ♦ psychiatric outpatients to be compelled to adhere to a care plan in accordance with Community Treatment Orders (see *Psychiatry*, PS51)
- Public Health legislation allows medical officers of health to detain, examine, and treat patients without their consent (e.g. a patient with TB refusing to take medication) to prevent transmission of communicable diseases (see *Population and Community Health*, PH4)

3. Special Situations

- public health emergencies (e.g. an epidemic or communicable disease treatment)
- warrant for information by police



Major Exceptions to Consent

- Emergencies
- Communicable diseases
- Mental Health legislation

Four Basic Requirements of Valid Consent

1. Voluntary

- consent must be given free of coercion or pressure
- the physician must not deliberately mislead the patient about the proposed treatment

2. Capable

- the patient must be able to understand the nature and effect of the proposed treatment

3. Specific

- the consent provided is specific to the procedure being proposed and to the provider who will carry out the procedure (i.e. the patient must be informed if students will be involved in providing the treatment)

4. Informed

- sufficient information must be provided to allow the patient to make choices in accordance with their wishes. This information should include:
 - ◆ the nature of the treatment or investigation proposed and its expected effects
 - ◆ all significant risks and special or unusual risks
 - ◆ alternative treatments or investigations and their anticipated effects and significant risks
 - ◆ the consequences of declining treatment
 - ◆ risks that are common sense need not be disclosed (i.e. bruising after venipuncture)
- **the reasonable person test** – the physician must provide all information that would be needed “by a reasonable person in the patient’s position” to be able to make a decision
 - ◆ disclose common adverse events (>1/200 chance of occurrence) and serious risks (e.g. death) even if remote
- it is the physician’s responsibility to make reasonable attempts to ensure that the patient understands the information
- physicians cannot withhold information about a therapeutic option based on personal conscience (e.g. not discussing the option of emergency contraception)



The Supreme Court of Canada expects physicians to disclose the risks that a “reasonable” person would want to know. In practice, this means disclosing minor risks that are common as well as serious risks that happen infrequently.

Consequences of Failure to Obtain Valid Consent

- treatment without consent is battery, even if the treatment is life-saving
- treatment of a patient on the basis of poorly informed consent may constitute negligence
- the onus of proof that valid consent was not obtained rests with the plaintiff (usually the patient)

Capacity and Substitute Decision Makers (see *Assessing Capacity*, ELOAM9)

- capable patients are entitled to make their own decisions
- capacity assessments must be conducted by a physician and, if appropriate, in consultation with other health care professionals (e.g. another physician, a mental health nurse)
- capable patients can refuse treatment even if it leads to serious harm or death; however, decisions that put patients at risk of serious harm or death require careful scrutiny



Consent

Treatment without consent = battery, including if NO consent or if **WRONG** procedure

Treatment with poor or invalid consent = negligence

Substitute Decision Makers (SDMs)

- SDM must follow the following principles when giving informed consent:
 - act in accordance with wishes previously expressed by the patient while capable
 - if wishes unknown, act in the patient’s best interest, taking the following into account:
 1. values and beliefs held by the patient while capable
 2. whether well-being is likely to improve with vs. without treatment
 3. whether the expected benefit outweighs the risk of harm
 4. whether a less intrusive treatment would be as beneficial as the one proposed
 - the final decision of the SDM may and should be challenged by the MD if the MD believes the SDM is not abiding by the above principles
- most provinces have legislated hierarchies for SDMs; the hierarchy in Ontario is:
 1. legally appointed guardian
 2. appointed attorney for personal care, if a power of attorney confers authority for treatment consent (see *Power of Attorney*, ELOAM4)
 3. representative appointed by the Consent and Capacity Board
 4. spouse or partner
 5. child (age 16 or older) or parent (unless the parent has only a right of access)
 6. parent with only a right of access
 7. sibling
 8. other relative(s)
 9. public guardian and trustee



If the MD feels the SDM is not acting in the patient’s best interest, the MD can apply to Consent and Capacity Board for another SDM.



Administration of treatment for an incapable patient in an emergency situation is applicable if the patient is:

1. Experiencing extreme suffering
2. At risk of sustaining serious bodily harm if treatment is not administered promptly

Treatment of the Incapable Patient

- obtain informed consent from SDM
- an incapable patient can only be detained against his/her will to receive treatment if he/she meets criteria for certification under the *Mental Health Act* (see *Psychiatry*, PS51). In such a situation:
 - document assessment in chart
 - notify patient of assessment using appropriate Mental Health Form(s) (Form 42)
 - notify Rights Advisor



There is no age of consent.

Pediatric Aspects of Capacity Covered by the HCCA

- no age of consent; consent depends on patient's decision-making ability (capacity) N.B. PEI, NB, QC, SK, BC have specific age of consent, but common law and case law deem underage legal minors capable, allowing them to make their own choices
- infants and children are assumed to lack mature decision-making capacity for consent but they should still be involved (i.e. be provided with information appropriate to their comprehension level)
- adolescents are usually treated as adults
- preferably, assent should still be obtained from patient, even if not capable of giving consent
- in the event that the physician believes the SDM is not acting in the child's best interest, an appeal must be made to the local child welfare authorities
- under normal circumstances, parents have right of access to the child's medical record

Criteria for Financial Competence

- covered by the *Mental Health Act* and *Substitute Decision Act*
- patient must:
 - appreciate importance of financial capability and reason for exam
 - have realistic appreciation of own strengths/weaknesses in managing finances
 - understand nature and extent of assets, liabilities, income, and expenses
 - have recently demonstrated ability to make reasonable financial decisions and be expected to do so in future
 - have appropriately used available resources and indicate willingness to do so in future
- if MD determines the patient incapable of managing property, a Form 21 is completed and the Public Guardian and Trustee becomes the temporary guardian until a substitute can be found; eligible substitute guardians are patient's spouse/partner, relative, or attorney
- Form 21 can only be filled out if the patient is an inpatient of a psychiatric facility; to continue financial incapacity after discharge, fill out Form 24



Other Types of Capacity Not Covered by the HCCA

- Testamentary (ability to make a will)
- Fitness (ability to stand trial)
- Financial (ability to manage property – Form 21 of the *Mental Health Act*)
- Personal (ability to care for oneself on a daily basis)

Instructional Advance Directives

- allow patients to exert control over their care once they are no longer capable
- the patient sets out their decisions about future health care, including who they would allow to make treatment decisions on their behalf and what types of interventions they would want
- takes effect once the patient is incapable with respect to treatment decisions
- in Ontario, a person can appoint a power of attorney for personal care to carry out his/her advance directives
- patients should be encouraged to review these documents with their family and physicians and to reevaluate them often to ensure they are current with their wishes



Power of Attorney (POA)

LEGAL TERMS AND DEFINITIONS

- all Guardians and Attorneys for Personal Care have fiduciary duties for the dependent person

Power of Attorney for Personal Care

- a legal document in which one person gives another the authority to make personal care decisions (health care, nutrition, shelter, clothing, hygiene, safety) on their behalf if they become mentally incapable

Guardian of the Person

- someone who is appointed by the Court to make decisions on behalf of an incapable person in some or all areas of personal care, in the absence of a POA for personal care

Continuing Power of Attorney for Property

- a legal document in which a person gives another the legal authority to make decisions about their finances if they become unable to make those decisions

Guardian of Property

- someone who is appointed by the Public Guardian and Trustee or the Courts to look after an incapable person's property or finances

Public Guardian and Trustee

- acts as a SDM of last resort on behalf of mentally incapable people who do not have another individual to act on their behalf

Confidentiality and Reporting Requirements

- the legal duty to maintain patient confidentiality is imposed by provincial health information legislation and precedent-setting cases in the common law
- the right to confidentiality is not absolute
- disclosure of health information can take place with the patient's consent or without the patient's consent in certain circumstances defined by statutory and common law

Statutory Reporting Obligations

- legislation has defined specific instances where public interest overrides the patient right to confidentiality; varies by province, but may include:
 1. suspected child abuse or neglect – report to local child welfare authorities (e.g. Children's Aid Society)
 2. fitness to drive a vehicle or fly an airplane – report to provincial Ministry of Transportation (see *Geriatric Medicine*, GM9)
 3. communicable diseases – report to local public health authority (see *Population and Community Health*, PH27)
 4. improper conduct of other physicians or health professionals – report to college or regulatory body of the health professional (sexual impropriety by physicians is required reporting in some provinces)
 5. vital statistics must be reported; reporting varies by province (in Ontario, births are required to be reported within 30 days to Office of Registrar General or local municipality; death certificates must be completed by a MD then forwarded to municipal authorities)
 6. reporting to coroners (see *Physician Responsibilities Regarding Death*, ELOAM20)
- physicians who fail to report in these situations are subject to prosecution and penalty, and may be liable if a third party has been harmed

Duty to Protect/Warn

- the physician has a duty to protect the public from a known dangerous patient; this may involve taking appropriate clinical action (e.g. involuntary detainment of violent patients for clinical assessment), informing the police, or warning the potential victim(s) if a patient expresses an intent to harm
- first established by a Supreme Court of California decision in 1976; supported by Canadian courts
- obliged by the CMA Code of Ethics and recognized by some provincial/territorial regulatory authorities
- concerns of breaching confidentiality should not prevent the MD from exercising the duty to protect; however, the disclosed information should not exceed that required to protect others
- applies in a situation where:
 1. there is a clear risk to identifiable person(s);
 2. there is a risk of serious bodily harm or death; and
 3. the danger is imminent (i.e. more likely to occur than not)

Disclosure for Legal Proceedings

- disclosure of health records can be compelled by a court order, warrant, or subpoena

Privacy of Medical Records

- privacy of health information is protected by professional codes of ethics, provincial and federal legislation, the *Canadian Charter of Rights and Freedoms*, and the fiduciary duty
- the federal government created the *Personal Information Protection and Electronic Documents Act* (PIPEDA), which established principles for the collection, use, and disclosure of information that is part of commercial activity (e.g. physician practices, pharmacies, private labs)
- PIPEDA has been superseded by provincial legislation in many provinces, such as the *Ontario Personal Health Information Protection Act*, which applies more specifically to health information

Duties of Physicians with Regards to the Privacy of Health Information

- inform patients of information-handling practices through various means (e.g. posting notices, brochures and pamphlets, and/or through discussions with patients)
- obtain the patient's express consent to disclose information to third parties
 - under Ontario privacy legislation, the patient's express consent needs not be obtained to share information between health care team members involved in the "circle of care." However, the patient may withdraw consent for this sharing of information.
- provide the patient with access to their entire medical record; exceptions include instances where there is potential for harm to the patient or a third party
- provide secure storage of information and implement measures to limit access to patient records
- ensure proper destruction of information that is no longer necessary



Legal Aspects of Confidentiality

Advice should always be sought from provincial licensing authorities and/or legal counsel when in doubt.

Ontario's Medical Expert Panel on Duty to Warn

Ferris et al., 1998

There should be a duty to inform when a patient reveals that he/she intends to do serious harm to another person(s) and it is more likely than not that the threat will be carried out.

Where a threat is directed at a person or group and there is a specific plan that is concrete and capable of commission and the method for carrying it out is available to the threatener, the physician should immediately notify the police and, in appropriate circumstances, the potential victim. The report should include the threat, the situation, the physician's opinion and the information upon which it is based.



CMA Code of Ethics

- Protect the health information of your patients.
- Provide information reasonable in the circumstances to patients about the reasons for the collection, use and disclosure of their health information.
- Be aware of your patient's rights with respect to the collection, use, disclosure and access to their health information; ensure that such information is recorded accurately.



Negligence and Liability

- **negligence**: breach of a legal duty of care which results in damage
 - legal finding, not a medical one
- physicians may be found negligent when the following four conditions are met:
 1. the physician owed a **duty of care to the patient** (the existence of a doctor-patient relationship generally suffices)
 2. the **duty of care was breached** (e.g. by failure to provide the **standard of care**)
 3. the patient was **injured or harmed**
 4. the harm or injury **was caused** by the breach of the duty of care
- the **standard of care** is one that would reasonably be expected under similar circumstances of an ordinary, prudent physician of the same training, experience, and specialization
- errors of judgement are not necessarily negligent
 - making the wrong diagnosis is not negligent if a reasonable doctor might have made the same mistake in the same circumstances
 - failure to reconsider the diagnosis if the patient does not respond to treatment may be negligent
- physicians can be held liable for the negligent actions of their employees or other individuals they are supervising



Physician Competence and Conduct

- the competence and conduct of physicians is legally regulated in certain respects to protect patients and society
- physicians are legally required to maintain a license with the appropriate authority
- physicians must ensure that patients have access to continuous on-call coverage and are never abandoned
- sexual conduct with patients, even when consented to by the patient, is a serious matter that can lead to criminal, civil, and disciplinary action
 - sexual conduct includes intercourse, undue touching, inappropriate reference to sexual matters, sexual jokes, and physician presence when capable patients undress or dress
 - physicians may have a personal relationship with a patient providing a year has passed since the last therapeutic contact
 - physicians are prohibited from personal relationships with patients whom they saw for psychotherapy
 - in Ontario, physicians must report any colleagues of whom they have information regarding sexual impropriety
- physicians must maintain adequate records for each patient, including:
 - showing that care has been continuous and comprehensive
 - minimal standards for record-keeping include diagnosis, differential diagnosis, appropriate tests and referrals, coherent patient record (full standards available at www.cpsso.on.ca)
 - keeping records for 10 years in most jurisdictions
 - although the medical record is the property of the physician or an institution, the patient or the patient's delegate must be allowed full access to information in the medical record upon (usually written) request
- in the hospital, physicians must ensure their own competence, respect hospital by-laws and regulations, practice only within the limits of granted privileges, cooperate with other hospital personnel, and maintain adequate hospital records



CMA Code of Ethics

Report any unprofessional conduct by colleagues to the appropriate authority.

Ethics



Principles of Ethics

- ethics deals with 1) the principles and values that help define what is morally right and wrong, and 2) the rights, duties and obligations of individuals and groups
- there are two broad approaches to ethics: **consequentialism** and **deontology**
 - consequentialism distinguishes right from wrong according to an action's outcomes (i.e. the right thing to do is minimize suffering) while deontology is rule or duty-based (i.e. it is always wrong to punish the innocent)
 - there is no one agreed upon ethical theory but most contemporary writers combine both approaches
 - most widely used approach is '**principlism**'

The Four Principles Approach to Medical Ethics ('principlism')

1. Respect for Autonomy

- recognizes an individual's right and ability to decide for themselves according to his/her beliefs and values
- respecting and promoting an individual patient's values in decision making to empower him or her
- a patient's decision may differ from the recommendation of the physician and the physician should understand, appreciate, and respect the patient's perspective
- patients are not expected to act in ways considered reasonable by others as long as they do not harm others (this principle is not applicable to newborn children or situations where informed consent and choice are not possible or may not be appropriate)
- autonomy also requires showing fidelity to incapable patients' prior capable views if known, and treating them with worth and dignity

2. Beneficence

- acting in the patient's 'best interests', where these represent the patient's values, beliefs, and preferences, so far as these are known
- the aim is to minimize harmful outcomes and maximize beneficial ones
- physicians recommend treatment based on evidence and professional experience to patients and help them weigh the risks and benefits of various options
- autonomy should be integrated with the physician's conception of a competent patient's best interests
- paramount in situations where consent/choice is not possible or may not be appropriate

3. Non-Maleficence

- obligation to avoid causing harm; *primum non nocere* ("First, do no harm")
- efforts should be made to reduce error and adverse events and ensure patient safety
- a limit condition of the Beneficence principle

4. Justice

- fair distribution of benefits and harms within a community, regardless of geography or privilege
- scarce resources are distributed based on the needs of patients and the benefit they would receive from obtaining a specific resource (e.g. organs for transplantation are fairly distributed if they go to those who are the most unwell, who are the most likely to survive the longest with the transplant, and who have waited the longest to receive a transplant)
- concept of fairness: Is the patient receiving what he/she deserves? How do treatment decisions impact on others?
- respects rules of fair play and basic human rights, such as freedom from persecution and the right to have one's interests considered and respected



Four Ethical Principles

1. Autonomy
2. Beneficence
3. Non-maleficence
4. Justice



Autonomy vs. Competence

Autonomy: the right that patients have to make decisions according to their beliefs and preferences

Competence: the ability or capacity to make a specific decision for one's self



Adverse Event (AE)

An unintended injury or complication from health care management resulting in disability, death or prolonged hospital stay.

The Canadian Adverse Events Study: The Incidence of Adverse Events among Hospital Patients in Canada

CMAJ 2004; 170(11):1678-86

Study: Review of random sample of charts in four randomly selected Canadian hospitals for the fiscal year 2000.

Patients: 4174 patient charts sampled, 3745 eligible charts (>18 years of age; nonpsychiatric, nonobstetric, minimum 24 hour admission).

Results: AE rate was 7.5% per 100 hospital admissions (95% CI 5.7-9.3). Highly preventable AEs occurred in 36.9% of patients with AEs (95% CI 32.0-41.8%) and death occurred in 20.8% (95% CI 7.8%-33.8%). An estimated 1521 additional hospital days were associated with AEs. Patients with AEs were significantly older than those without (mean age [and standard deviation] 64.9 [16.7] v. 62.0 [18.4] years; $p=0.016$). Men and women experienced equal rates of AEs.

Conclusions: The overall incidence rate of AEs of 7.5% suggests that, of the almost 2.5 million annual hospital admissions in Canada similar to the type studied, about 185 000 are associated with an AE and close to 70 000 of these are potentially preventable.



Code of Ethics

- the CMA has developed and approved a **Code of Ethics** that acts as a common ethical framework for Canadian physicians
 - sources include the Hippocratic Oath, developments in human rights, recent bioethical discussion
 - may set out different standards of behaviour than does the law
 - prepared by physicians for physicians
 - based on the fundamental ethical principles of medicine
 - statements are general in nature
 - applies to physicians, residents, and medical students



The CMA Code of Ethics is a quasi-legal standard for physicians. If the law sets a minimal moral standard for doctors, the Code ratchets up these standards.

- **CMA policy statements** address specific ethical issues not mentioned by the code (e.g. abortion, transplantation, and euthanasia)
- the American Medical Association (AMA) has a **Code of Medical Ethics**
 - articulates the values of medicine as a profession
 - defines medicine's integrity and is the source of the profession's authority to self-regulate
 - considered an evolving document that changes as new questions arise concerning medicine's core values and its application to daily practice
- the AMA develops policy positions ("AMA Policy") regarding health care issues, the health care system, internal organizational structure, decision-making processes, and medical science and technology



Confidentiality



Reasons to Breach Confidentiality

- Child abuse
- Fitness to drive
- Communicable disease
- Coroner report
- Duty to inform/warn



CMA Code of Ethics

"Disclose your patients' personal health information to third parties only with their consent, or as provided for by law, such as when the maintenance of confidentiality would result in a significant risk of substantial harm to others or, in the case of incompetent patients, to the patients themselves. In such cases take all reasonable steps to inform the patients that the usual requirements for confidentiality will be breached."

- a full and open exchange of information between patient and physician is central to a therapeutic relationship
- privacy is a **right** of patients (which they may forego), while confidentiality is a **duty** of doctors (which they must respect barring patient consent or the requirements of the law)
- if inappropriately breached by a doctor, he/she can be sanctioned by the hospital, by the court or by his or her regulatory authority (see *Confidentiality and Reporting Requirements*, ELOAM5)
- based on the ethical principal of patient autonomy, patients have the right to:
 - control their own information
 - expect information concerning them will receive proper protection from unauthorized access by others (see *Privacy of Medical Records*, ELOAM5)
- **confidentiality may be ethically and legally breached in certain circumstances**, e.g. the threat of harm to others (see *Confidentiality and Reporting Requirements*, ELOAM5)
- unlike the solicitor-client privilege, there is no 'physician-patient privilege' by which a physician, even a psychiatrist, can promise the patient absolute confidentiality
- physicians should seek advice from their local health authority or the Canadian Medical Protective Association (CMPA) before disclosing HIV status of a patient to someone else
 - many jurisdictions make mandatory not only the reporting of serious communicable diseases (e.g. AIDS), but also the reporting of those who harbour the agent of the communicable disease
 - physicians failing to abide by such regulations could be subject to professional or civil actions



Consent



CPSO Policy Consent

Obtaining valid consent before carrying out medical, therapeutic and diagnostic procedures has long been recognized as an elementary step in fulfilling the doctor's obligations to the patient.

- the autonomous authorization of a medical intervention by a patient
- applies to acceptance and refusal of treatment
- also see *Consent under the Law*, ELOAM2

Ethical Principles Underlying Consent

- usually the principle of respect for patient autonomy overrides the principle of beneficence
- where a patient cannot make an autonomous decision, it is the duty of the SDM (or the physician in an emergency) to act on the patient's known prior wishes or, failing that, to act in the patient's best interests
- there is a duty to discover, if possible, what the patient would have wanted when capable
- central to determining best interests is understanding the patient's values, beliefs, and cultural or religious background since these may affect the patient's perception of treatments as beneficial or harmful
- more recently expressed wishes should take priority over remote ones
- patient preferences may be given orally (i.e. do not have to be in written form)

Obtaining Consent

- a signed consent form only documents the consent – it does not replace the process for obtaining valid consent (see Figure 1)
- what matters is what the patient understands and appreciates, not what the signed consent form states
- consent can be withdrawn at any point, unless stopping a procedure would put the patient at risk of serious harm
- consent is not required in certain situations (see *Consent under the Law*, ELOAM2)

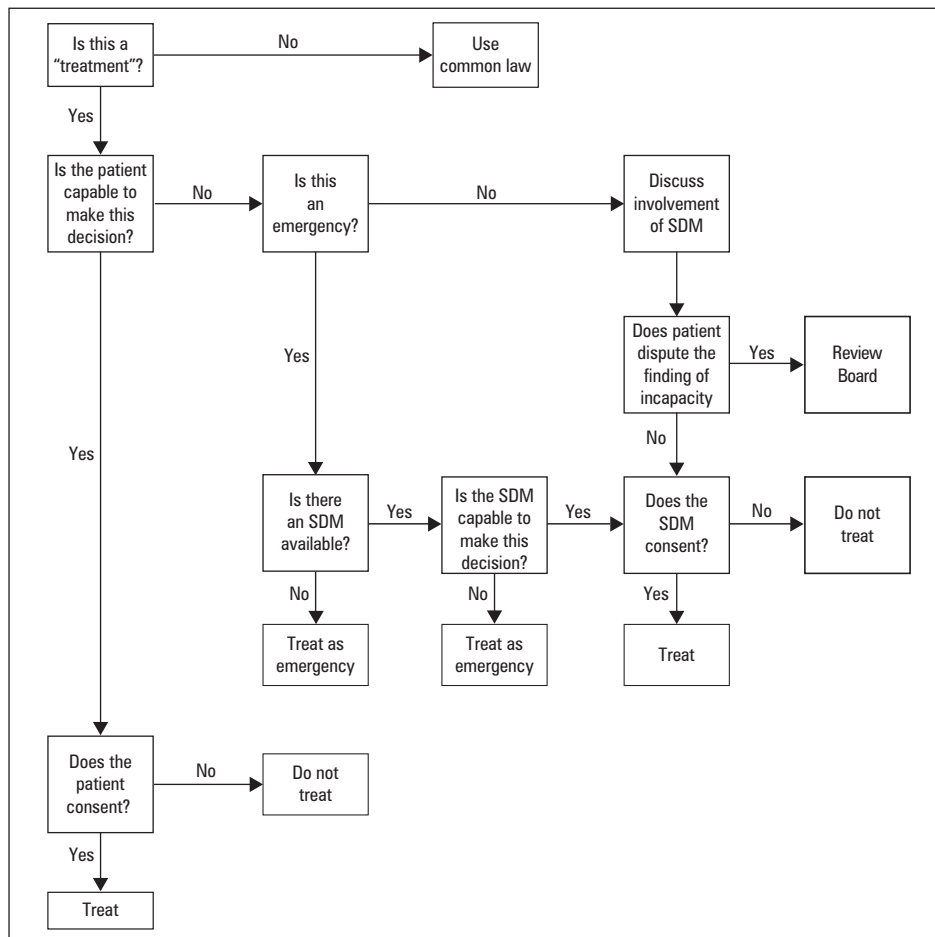


Figure 1. Consent Flowchart

SDM = substitute decision maker

Adapted by P. Hébert from Sunnybrook Health Sciences Centre Consent Guidelines

Assessing Capacity

- a person is presumed capable unless there is good evidence to the contrary
- capacity is the ability to:
 - understand information relevant to a treatment decision
 - appreciate the reasonably foreseeable consequences of a decision or lack of a decision
- **capacity is specific** for each decision (e.g. a person may be capable to consent to having a chest x-ray, but not for a bronchoscopy)
- most Canadian jurisdictions distinguish capacity to make health care decisions from capacity to make financial decisions. A patient may be deemed capable of one, but not the other.
- **capacity can change over time** (e.g. temporary incapacity secondary to delirium)
- clinical capacity assessment may include:
 - specific capacity assessment (i.e. capacity specific to the decision at hand)
 1. effective disclosure of information and evaluation of patient's reason for decision
 2. understanding of:
 - his/her condition
 - the nature of the proposed treatment
 - alternatives to the treatment
 - the consequences of accepting and rejecting the treatment
 - the risks and benefits of the various options (test: can the patient recite back what you have disclosed?)
 3. for the **appreciation** needed for decision making capacity, a person must:
 - acknowledge the condition that affects him/herself
 - be able to assess how the various options would affect him or her
 - be able to reach a decision and adhere to it, and make a choice, not based primarily upon delusional belief (test: are their beliefs responsive to evidence?)
 - general impressions
 - input from psychiatrists, neurologists, etc.
- employ "Aid to Capacity Evaluation" (see Table 1)



CPSO Policy Capacity

Capacity is an essential component of valid consent, and obtaining valid consent is a policy of the CMA and other professional bodies.

Table 1. Aid to Capacity Evaluation

Ability to understand the medical problem
Ability to understand the proposed treatment
Ability to understand the alternatives (if any) to the proposed treatment
Ability to understand the option of refusing treatment or of it being withheld or withdrawn
Ability to appreciate the reasonably foreseeable consequences of accepting the proposed treatment
Ability to appreciate the reasonably foreseeable consequences of refusing the proposed treatment
Ability to make a decision that is not substantially based on delusions or depression

Adapted from *Etchells et al.* (1996).

- a decision of incapacity may warrant further assessment by psychiatrist(s), legal review boards (e.g. in Ontario, the Consent and Capacity Review Board), or the courts
- judicial review is open to patients if found incapable
- see *Consent under the Law*, ELOAM2
- ethical principles underlying capacity
 - patient autonomy and respect for persons
 - physician beneficence requires that incapable persons be protected from making harmful decisions
 - even patients found incapable to make a specific decision should still be involved in that decision as much as possible (seek assent and cooperation and explore reasons for dissent)
 - people should be allowed to make their own informed decisions, or to appoint their own SDM
 - agreement or disagreement does not equal capacity



Truth Telling

Ethical Basis

- helps to promote and maintain a trusting physician-patient relationship
- patients have a right to be told important information that physicians have regarding their care
- enables patients to make informed decisions about health care and their lives

Legal Basis

- required for valid patient consent (see *Consent under the Law*, ELOAM2)
 - goal is to disclose information that a reasonable person in the patient's position would need in order to make an informed decision ("standard of disclosure")
- withholding information can be a breach of fiduciary duty and duty of care
- obtaining consent on the basis of misleading information can be seen as negligence

Evidence about Truth Telling

- most patients want to know what is wrong with them
- although many patients want to protect family members from bad news, they themselves would want to be informed in the same situation
- truth telling improves compliance and health outcomes
- informed patients are more satisfied with their care
- negative consequences of truth telling can include decreased emotional well-being, anxiety, worry, social stigmatization, and loss of insurability

Challenges in Truth Telling

- **medical error**
 - many jurisdictions and professional associations expect and require physicians to disclose medical error; any event that harms or threatens to harm patients must be disclosed to the patient or the patient's family and reported to the appropriate health authorities
 - physicians should disclose to patients the occurrence of adverse events or errors caused by medical management, but should not suggest that they resulted from negligence because:
 - a) negligence is a legal determination and b) error is not equal to negligence (see *Negligence and Liability*, ELOAM6)
 - disclosure allows the injured patient to seek appropriate corrective treatment promptly
 - ♦ physicians should avoid simple attributions as to cause and sole responsibility of others or oneself
 - ♦ physicians should offer apologies or empathic expressions of regret ("I wish things had turned out differently") as these can increase trust and are not admissions of guilt or liability
 - ♦ uniform *Apology Acts* across Canada protect apologies, both as expressions of regret and admissions of responsibility, from being used as evidence of liability and negligence
- **breaking bad news**
 - adequate support should be provided along with the disclosure of difficult news
 - SPIKES protocol was developed to facilitate "breaking bad news"



CPSO Policy Truth Telling

Physicians should provide patients with whatever information that will, from the patient's perspective, have a bearing on medical decision-making and communicate that information in a way that is comprehensible to the patient.



Protocol to Break Bad News: SPIKES

S **Setting** the scene and listening skills
P patient's **perception** of condition and seriousness
I **Invitation** from patient to give information
K **Knowledge** – giving medical facts
E **Explore** emotions and empathize
S **Strategy** and **summary**

WF Baile and R Buckman, 2000.

Arguments Against Truth Telling

- may go against certain cultural norms and expectations
- may lead to patient harm and increased anxiety
- 10-20% of patients prefer not to be informed
- medical uncertainty may result in the disclosure of uncertain or inaccurate information

Exceptions to Truth Telling

- waiving the right to know: patient declines information that would normally be disclosed
- physicians should explore such decisions and determine if patient is capable
- strong cultural or ethnic preferences for withholding information should be explored with the patient and it should be ascertained if the patient subscribes to these preferences
- if patients continue to decline important information, the patient's consent to inform someone else on their behalf should be sought
- a patient may waive their right to know the truth about their situation when
 - disclosure would in itself cause physical or mental harm to the patient
 - a strong cultural component exists that must be respected and acknowledged
 - the patient is incapacitated
 - he/she is in a medical emergency
 - the more weighty the consequences for the patient from non-disclosure, the more carefully one must consider the right to ignorance; arguably, such a patient could be considered as incapacitated and a SDM may need to be found to whom disclosure can be made
- the doctrine of therapeutic privilege is rarely acceptable in Canadian courts
 - refers to the withholding of information by the clinician in the belief that disclosure of the information would lead to anxiety, psychological distress or even self-harm. Such concerns have been found to be exaggerated and should not be grounds to deceive patients.
 - clinicians should avoid invoking therapeutic privilege and allow patients to make decisions based on an accurate description of their medical situation

Resource Allocation

- the distribution of goods and services to programs and people
- physicians have the duty to inform patients about therapeutic options even if they are not available
- ethics relate to **justice**: physicians must make health care resources available to patients in a manner which is fair and equitable, without bias or discrimination
 - need and benefit are morally relevant criteria for resource allocation
 - gender, sexual orientation, religion, level of education or age alone are morally irrelevant criteria
- ethical **dilemmas** that arise when deciding how best to allocate resources
 - fair chances versus best outcome – favouring best outcome vs. giving all patients fair access to limited resources (e.g. transplant list prioritization)
 - priorities problem – how much priority should treating the sickest patients receive?
 - aggregation problem – modest benefits to many vs. significant benefits to few
 - democracy problem – when to rely on a fair democratic process as the only way to arrive at a decision
- guidelines for appropriately allocating resources
 - the physician's primary obligation is to protect and promote the welfare and best interests of his or her patients
 - choose interventions known to be beneficial on the basis of evidence of effectiveness
 - seek the tests or treatments that will accomplish the diagnostic or therapeutic goal for the least cost
 - advocate for one's patients but avoid manipulating the system to gain unfair advantage for them
 - resolve conflicting claims for scarce resources justly, on the basis of morally relevant criteria such as need and benefit, using fair and publicly defensible procedures
 - inform patients of the impact of cost constraints on care, but in a sensitive way
 - seek resolution of unacceptable shortages at the level of hospital management or government



CPSO Policy Resource Allocation
Physicians should "recognize [their] responsibility to promote fair access to health care resources" and should "use health care resources prudently."



Research Ethics



Guiding Principles for Research Ethics

1. **Respect for persons**
(i.e. informed consent)
2. **Beneficence**
(i.e. balancing benefits and harms)
3. **Justice**
(i.e. avoiding exploitation or unjustified exclusion)

- involves the systematic analysis of ethical dilemmas arising during research involving human subjects to ensure that:
 - study participants are protected
 - clinical research is conducted to serve the interests of the participants and/or society as a whole
- major ethical dilemmas arise when a physician's obligation to the patient comes into conflict with other obligations and incentives
- any exceptions to disclosure for therapeutic consent do not apply in an experimental situation

Table 2. Ethical Principles for Research Involving Human Subjects

Patient's participation in research should not put him/her at a known or probable disadvantage with respect to medical care

Participant's voluntary and informed choice is usually required

Consent may not be required in special circumstances: chart reviews without patient contact; emergency situations for which there is no accepted or helpful standard of care and the proposed intervention is not likely to cause more harm than such patients already face

Access to the treatment that is considered standard

Placebo-controlled trials are generally acceptable where patients still receive the standard of care and are informed about the placebo arm and what that entails

Must employ a scientifically valid design to answer the research question

Scientific rigour ensured via peer review, expert opinion

Must demonstrate sufficient value to justify the risk posed to participants

Must be conducted honestly (i.e. carried out as stated in the approved protocol)

Findings must be reported promptly and accurately without exaggeration, to allow practicing clinicians to draw reasonable conclusions

Patients must not be enticed into risky research by the lure of money and investigators must not trade the interests of patients for disproportionate recompense by a sponsor; both participants and investigators are due fair recompense for their time and efforts

Any significant interventional trial ought to have a data safety monitoring board that is independent of the sponsor and can ensure safety of the ongoing trial

Laid out in the Declaration of Helsinki, the Belmont Report, etc.



Informed Consent for Research

- The nature of informed consent differs in the contexts of research and clinical practice in that the potential research subject must be informed about:
 - Purpose of the study
 - Source of funding
 - Nature and relative probability of harms and benefits
 - Nature of the physician's participation including any compensation
- Proposals for research must be submitted to a research ethics board to be scientifically and ethically evaluated and approved.



Physician-Industry Relations

- health care delivery in Canada involves collaboration between physicians and the pharmaceutical and health supply industries in the areas of research, education, and clinical evaluation packages (e.g. product samples)
- physicians have a responsibility to ensure that their participation in such collaborative efforts is in keeping with their duties to their patients and society
- gifts or free products from the pharmaceutical industry are inappropriate
 - sponsorship for travel and fees for conference attendance may be accepted only where the physician is a conference presenter and not just in attendance
 - physicians receiving such sponsorship must disclose this at presentations or in written articles
- CMA and CPSO guidelines for ethically appropriate physician-industry relations
 - the primary goal should be the advancement of the health of Canadians
 - relationships should be guided by the *CMA Code of Ethics*
 - the physician's primary obligation is to the patient
 - physicians should avoid any self-interest in their prescribing and referral practices
 - physicians should always maintain professional autonomy, independence, and commitment to the scientific method
- the *AMA Code of Medical Ethics* has a number of opinions on "Practice Matters" including "Industry representatives in clinical settings," "Financial incentives and the practice of medicine," and "Gifts to physicians from industry," (see www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics.shtml)



Doctor-Patient Relationship

- a partnership based on the physician providing expert opinion, information, options, and interventions that allows the patient to make informed choices about their health care
- within this relationship, the doctor and patient share the goals of positive health outcomes, good communication, honesty, flexibility, sensitivity, informed consent, and respect
- this relationship has the potential to be unequal due to a power difference
 - patients are ill and lack medical knowledge
 - physicians possess medical knowledge and skills and have their patients' trust

- due to the nature of the doctor-patient relationship, the physician will:
 - place the best interests of the patient first
 - establish a relationship of trust with the patient
 - follow through on undertakings made to the patient in good faith
- the physician will accept or refuse patients requesting care:
 - without consideration of race, gender, age, sexual orientation, financial means, religion or nationality
 - without arbitrary exclusion of any particular group of patients, such as those known to be difficult or afflicted with serious disease
 - except in emergency situations, in which case care must be rendered
- once having accepted a patient into care, the physician may terminate the relationship providing:
 - it is not an emergency
 - care has been transferred
 - adequate notice has been given to allow the patient to make alternative arrangements
 - they have other options to find 'medically necessary care'
- the physician will not exploit the doctor-patient relationship for personal advantage – financial, academic or otherwise
- the physician will disclose limitations to the patient where personal beliefs or inclinations limit the treatment the physician is able to offer
- the physician will maintain and respect professional boundaries at all times
 - including physical, emotional, and sexual boundaries
 - regarding treatment of themselves, their families, and friends



CPSO Policy: Treating Self and Family Members

Physicians will not diagnose or treat themselves or family members except for minor conditions or in emergencies and then only if no other physician is readily available.



CPSO Policy: Ending the Physician-Patient Relationship

Discontinuing services that are needed is an act of professional misconduct unless done by patient request, alternative services are arranged, or adequate notice has been given.

Personal and Professional Conduct

CanMEDS Competencies

- a framework of professional competencies established by the Medical Council of Canada (MCC) as objectives for the Medical Council of Canada Qualifying Exam (MCCQE)
- further information on MCC objectives can be found at www.mcc.ca

1. Communicator; Culturally Aware

- display sensitivity to people of all ages, races, cultures, religions, sexual orientations, and genders
- accept or refuse patients without consideration of age, race, culture, religion, sexual orientation, and gender
- understand the variation in values and morals and their impact on approaches to care and decision-making
- elicit patients' beliefs, concerns, and expectations about their illness
- conduct patient-centered interviews, ensure patient comprehension

2. Collaborator

- respect all members of the health care team
- identify the roles and competencies of each member, and delegate tasks appropriately
- consult other physicians and health care professionals effectively and appropriately
- consult with patients and families regarding continuing care plans
- be able to outline co-ordination of services (e.g. Public Health, Home Care, Social Services, Workers' Compensation, Children's Aid Society, etc.)

3. Health Advocate

- identify determinants of health:
 - biological (e.g. genes, impact of lifestyle)
 - physical (e.g. food, shelter, working conditions)
 - social (education, employment, culture, access to care)
- influence public health and health policy to protect, maintain, and promote the health of individuals and the community

4. Manager

- meet regulatory requirements in an office practice (e.g. medical record-keeping, narcotic control, infection control, etc.)
- be prudent in utilization of health care resources, based on anticipated cost-benefit balance
- regulate work schedule such that time is available for continuing education

5. Professional

- maintain standards of excellence in clinical care and ethical conduct
- exhibit appropriate personal and interpersonal behaviour
- enhance clinical competence through lifelong learning
- accept responsibility for personal actions
- do not exploit the physician-patient relationship for personal advantage (e.g. financial, academic)

6. Scholar

- commitment to critical appraisal, constructive skepticism
- participate in the learning of peers and others (e.g. students, health care professionals, patients)



Professional Considerations

Elderly Patient

- Identify their resuscitation options (CPR vs. DNR), if applicable
- Check for documentation of advance directives and POA where applicable
- For further details, see [Geriatric Medicine, GM11](#)

Pediatric Patient

- Identify the primary decision-maker (parents, guardian, wards-of-state, emancipated)
- Regarding capacity assessment see *Pediatric Aspects of Capacity Covered by the HCCA (ELOAM4)*
- Be wary of custody issues if applicable

Terminally Ill or Palliative Patient

- Consider the SPIKES approach to breaking bad news
- What are their goals of care, i.e. disease vs. symptom management?
- Identify advance directives, POA, or SDM, if applicable
- Check for documentation of resuscitation options (CPR vs. DNR) and likelihood of success
- For further details, see [Geriatric Medicine, GM11](#)

Incapable Patient

- If not already present, perform a formal capacity assessment
- Identify if the patient has a SDM or who has their POA
- Check the patient's chart for any Mental Health Forms (e.g. Form 1) or any forms they may have on their person (e.g. Form 42)



Areas of Controversy



Dealing with Controversial and Ethical Issues in Practice

- Discuss in a non-judgmental manner
- Ensure patients have full access to relevant and necessary information
- Identify if certain options lie outside of your moral boundaries and refer to another physician if appropriate
- Consult with appropriate ethics committees or boards
- Protect freedom of moral choice for students or trainees

Source: MCC-CLEO Objectives, 1998



Euthanasia: Ethically Appropriate Actions

- Respect competent decisions to forgo treatment
- Provide appropriate palliative measures
- Decline requests for euthanasia and assisted suicide

Euthanasia and Physician-Assisted Suicide

- **euthanasia**: a deliberate act undertaken by one person with the intention of ending the life of another person to relieve that person's suffering where the act is the cause of death
- **physician-assisted suicide**: the act of intentionally killing oneself with the assistance of a physician who deliberately provides the knowledge and/or the means
- ethical issues and arguments:
 - right to make autonomous choices about the time and manner of own death
 - belief that there is no ethical difference between the acts of euthanasia/assisted suicide and foregoing life-sustaining treatments
 - belief that these acts benefit terminally ill patients by relieving suffering
 - patient autonomy has limits
 - death should be the consequence of the morally justified withdrawal of life-sustaining treatments only in cases where there is a fatal underlying condition, and it is the condition (not the withdrawal of treatment) that causes death
- law
 - Canada: euthanasia and physician-assisted suicide are punishable offences under the Criminal Code of Canada
 - US: euthanasia is punishable under general homicide laws; Oregon and Washington are the only states to have enacted legislation allowing physicians to actively assist patients who wish to end their lives
- the use of palliative sedation with opioids in end-of-life care, knowing that death may occur as an unintended consequence (**principle of double effect**) is distinguished from euthanasia and assisted suicide where death is the primary intent
- the appropriate withdrawal of life-support is distinguished from euthanasia and assisted suicide as it is seen as allowing the underlying disease to take its 'natural course'

Maternal-Fetal Conflict of Rights

- conflict between maternal autonomy and the best interests of the fetus
- ethical issues and arguments
 - principle of reproductive freedom: women have the right to make their own reproductive choices
 - coercion of a woman to accept efforts to promote fetal well-being is an unacceptable infringement of her personal autonomy
- law: upholds a woman's right to life, liberty, and security of person and does not recognize fetal rights
 - if a woman is competent and refuses medical advice, her decision must be respected even if the fetus will suffer
 - the fetus does not have legal rights until it is born alive and with complete delivery from the body of the woman
- *Royal Commission on New Reproductive Technologies* recommendations:
 - medical treatment must never be imposed upon a competent pregnant woman against her wishes
 - no law should be used to confine a pregnant woman in the interest of her fetus
 - the conduct of a pregnant woman in relation to her fetus should not be criminalized
 - child welfare should never be used to control a woman's behaviour during pregnancy
 - civil liability should never be imposed upon a woman for harm done to her fetus during pregnancy
- ethically appropriate actions
 - a woman is permitted to refuse HIV testing during pregnancy, even if vertical transmission to fetus results
 - a woman is permitted to refuse Caesarean section in labour that is not progressing, despite evidence of fetal distress



Advanced Reproductive Technologies: Ethically Appropriate Actions

- Educate patients and address contributors to infertility (e.g. stress, alcohol, medications, etc.)
- Investigate and treat underlying health problems causing infertility
- Wait at least one year before initiating treatment with ART (exceptions – advanced age or specific indicators of infertility)
- Educate and prepare patients for potential negative outcomes of ART

Advanced Reproductive Technologies (ART)

- includes non-coital insemination, hormonal ovarian stimulation, and *in vitro* fertilization (IVF)
- ethical issues and arguments
 - donor anonymity vs. child-centred reproduction (i.e. knowledge about genetic medical history)
 - preimplantation genetic testing for diagnosis before pregnancy
 - lack of sufficient data regarding efficacy and complications to provide the full disclosure needed for truly informed consent
 - use of new techniques without patients appreciating their experimental nature
 - embryo status – the Supreme Court of Canada maintains that fetuses are “unique” but not persons under law; this view would likely apply to embryos as well
 - access to ART
 - ♦ private vs. public funding
 - ♦ social factors limiting access to ART (e.g. same-sex couples)
 - commercialization of reproduction; reimbursement of gamete donors is currently illegal in Canada

Fetal Tissue

- pluripotent stem cells have been derived from human embryonic and fetal tissue
- potential uses of stem cells in research:
 - studying human development and factors that direct cell specialization
 - evaluating drugs for efficacy and safety in human models
 - cell therapy: using stem cells grown *in vitro* to repair or replace degenerated/destroyed/malignant tissues (e.g. Parkinson's disease)
 - genetic treatment aimed at altering somatic cells (i.e. myocardial or immunological cells) is acceptable and ongoing
 - genetic treatment aimed at altering germ cells is prohibited in Canada and elsewhere
- *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Government of Canada, 2003)
 - embryo research is permitted up to 14 days post-fertilization
 - embryos created for reproductive purposes that are no longer required may be used
 - gamete providers must give free and informed consent for research use
 - no commercial transactions in the creation and use of the embryos is permitted
 - creation of embryos solely for research purposes is prohibited
 - human cloning is strictly prohibited
- risks of coercion must be minimized:
 - may not pressure fertility treatment team to generate more embryos than necessary
 - only discuss option of using fetal tissue for research after free and informed choice to have a therapeutic abortion has been made
 - physicians responsible for fertility treatment may not be part of a stem cell research team



The CMA remains neutral on the issue of embryonic stem cell research.

Abortion

- abortion: the active termination of a pregnancy before fetal viability
 - **fetal viability:** fetus >500 g, or >23-24 weeks gestational age
 - in the case of multiple pregnancy, selective termination of the non-viable or less viable fetus is allowed
- ethical and legal issues and arguments:
 - according to common law, the rights of a fetus are not equal to those of a human being
 - who should have input into the abortion decision (e.g. male partners, patient's guardians)
 - ♦ no law currently regulates abortion in Canada – it is a woman's medical decision to be made in consultation with whom she wishes; no mandatory role for spouse/family
- CMA policy on induced abortion:
 - induced abortion should not be used as an alternative to contraception
 - counselling on contraception must be readily available
 - full and immediate counselling services must be provided in the event of unwanted pregnancy
 - there should be no delay in the provision of abortion services
 - no patient should be compelled to have a pregnancy terminated
 - physicians should not be compelled to participate in abortion – if morally opposed, the physician should inform the patient so she may consult another physician
 - no discrimination should be directed towards either physicians who do not perform or assist at induced abortions or physicians who do
 - induced abortion should be uniformly available to all women in Canada and health care insurance should cover all the costs (N.B. the upper limit of gestational age for which coverage is provided varies between provinces)

Genetic Testing

- uses:
 - confirm a clinical diagnosis
 - detect genetic predisposition to a disease
 - ♦ allows preventative steps to be taken and helps patient prepare for the future
 - give parents the option to terminate a pregnancy or begin early treatment
- ethical dilemmas arise because of the nature of genetic information:
 - it has individual and familial implications
 - it pertains to future disease
 - it often identifies disorders for which there are no effective treatments or preventive steps
- ethical issues and arguments:
 - obtaining informed consent is difficult due to the complexity of genetic information
 - doctor's duty to maintain confidentiality vs. duty to warn family members
 - risk of social discrimination (e.g. insurance) and psychological harm
- law:
 - no current specific legislation exists
 - testing requires informed consent
 - no standard of care exists for clinical genetics but physicians are legally obligated to inform patients that prenatal testing exists and is available
 - breach of confidentiality – duty to warn family members
 - ♦ only acceptable if can likely prevent serious harm, such as if treatment or prevention is available (e.g. familial adenomatous polyposis)



Genetic Testing: Ethically Appropriate Actions

- Thorough discussion and realistic planning with patient before testing is done
- Genetic counselling for delivery of complex information, supportive discussion

Organization of Health Care in Canada

- one federal, three territorial, and ten provincial systems
- federal system provides care to Aboriginal groups, the RCMP, and the armed forces
- financed by both the public (70%) and private (30%) sectors
- each provincial plan must cover all medically necessary health services delivered in hospitals and by physicians; may choose to cover additional services such as home care and prescription drugs
- non-insured health services and fees are either covered by private insurance or by the individual
- workers' compensation funds cover treatment for work-related injuries and diseases

The current legal foundation of the Canadian health system is based on three statutes:

1. **Constitution Act** (1867) – deals primarily with the jurisdictional power between federal and provincial governments
2. **Canada Health Act** (1984) – outlines the national terms and conditions
3. **Canada Health and Social Transfer Act** (1996) – sets the conditions for fiscal transfers from the federal government to the provinces and territories



History

- 1867 *British North America Act* (now *Constitution Act*) establishes Canada as a confederacy
 - government has minimal role in health care at this time
 - “establishment, maintenance, and management of hospitals” under provincial jurisdiction
- 1947 Saskatchewan introduces universal hospital insurance
 - based on taxes and premiums
 - other provinces follow
- 1957 Federal government passes *Hospital Insurance and Diagnostic Services Act*
 - provinces with universal hospital insurance receives federal funds
 - federal government pays for approximately 50% of insured services
- 1962 Saskatchewan implements universal medical care insurance
 - physician services included
- 1965 *Royal Commission on Health Services (Hall Commission)* recommends federal leadership and financial support with provincial government operation
- 1966 **Medical Care Act** passed by federal government
 - federal government contribution maintained at 50% on average, with poorer provinces receiving more funds
 - medical insurance must be
 - Comprehensive ▪Portable
 - Universal▪Publicly administered
- 1977 *Established Programs Financing Act* passed by federal government
 - federal government gives “tax points” to provinces by reducing federal taxes and allowing provinces to collect more
 - funding no longer tied to direct services → federal influence wanes
 - provinces bear greater costs and impose restrictions on physicians
 - physicians respond with “extra-billing:” patients pay a supplementary fee
- 1984 **Canada Health Act** passed by federal government
 - replaced *Medical Care Act* and *Hospital Insurance and Diagnostic Services Act*
 - extra-billing banned by new fifth criterion: **Accessibility**
- 1996 *Canada Health and Social Transfer Act* passed by federal government
 - federal government gives provinces a single grant for health care, social programs, and post-secondary education; division of resources at provinces' discretion
- 1999 *Social Union Framework Agreement* signed by the Prime Minister and all Premiers and territorial leaders except Quebec
 - federal and provincial/territorial governments vow to concentrate their efforts to modernize Canadian social policy
- 2001 *Kirby and Romanow Commissions* appointed
 - Kirby Commission* (final report, October 2002)
 - one-member committee of the Senate: examined history of health care system in Canada, pressures and constraints of current health care system, role of federal government, and health care systems in foreign jurisdictions
 - Romanow Commission* (final report, November 2002)
 - one-member royal commission (former Saskatchewan Premier Roy Romanow) appointed by the Prime Minister to inquire into and undertake dialogue with Canadians on the future of Canada's public health care system

- 2003 *First Ministers' Accord on Health Care Renewal* signed
- First Ministers agreed on an action plan to improve access to quality care for all Canadians and to prepare an annual public report on primary and home care
 - 1st Health Council (composed of government and expert/public representatives) appointed to improve accountability in the health care system
- 2004 *First Ministers' Meeting on the Future of Health Care* produces a 10-year plan
- priorities include reductions in waiting times, development of a national pharmacare plan, and primary care reform
- 2005 *Chaoulli v. Quebec*, Supreme Court of Canada Decision
- ruled that banning private insurance is unconstitutional under the Quebec Charter of Rights, given that patients do not have access to those services under the public system in a timely way

Key Principles of the *Canada Health Act*

1. Public Administration

- provincial health care programs must be administered by public authorities

2. Comprehensiveness

- provincial health care programs must cover all necessary diagnostic, physician, and hospital services

3. Universality

- all eligible residents must be entitled to health care services

4. Portability

- emergency health services must be available to Canadians who are outside their home province, paid for by the home province

5. Accessibility

- user fees, charges, or other obstructions to insured health care services are not permitted



The federal government can reduce its contributions to provinces that violate the key principles of the *Canada Health Act*.

Health Care Expenditure and Delivery in Canada

- projected total health care expenditure in 2006 was \$148 billion, 10.0% of the GDP, approx. \$3678 USD per capita; this includes out-of-pocket, government-funded and third-party expenditures (*Canadian Institute of Health Information*)
- the 2006 Canadian health care expenditure increased 5.8% over 2005 spending (*Canadian Institute of Health Information*)
- the 2006 Canadian health care expenditure as a percentage of GDP ranked eighth out of 30 Organization for Economic Cooperation and Development (OECD) member nations
- 70.4% of health care spending came from public sector sources in 2006, as compared to 45.8% in the US
- in 2006 there were 2.1 physicians per 1000 population, ranking 26th out of OECD member countries

Payments for Care at Private For-Profit and Private Not-for-Profit Hospitals:

A Systematic Review and Meta-analysis

CMAJ 2004; 170(12):1817-24

Meta-analysis of 8 US observational studies involving more than 350 000 patients. Concluded that care provided by private for-profit hospitals was more expensive (Relative payments for care=1.19; 95% CI=1.07-1.33; p=0.001). If half of Canadian hospitals were converted to private for-profit institutions, an extra \$3.6 billion would be paid annually.

Delivery of Health Care

- hospital services in Canada are publicly funded but delivered through private, not-for-profit institutions owned and operated by communities, religious organizations, and regional health authorities
- this differs from other countries, such as the US (a mix of public and private funding, as well as private-for-profit and private not-for-profit delivery) and the UK (primarily public funding and delivery)

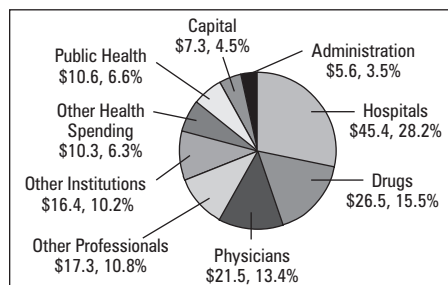


Figure 2. Health Expenditure in Canada by Use of Funds (Billions of Dollars), 2007

Source: Canadian Institute for Health Information, *National Health Expenditure Trends, 1975 to 2009*

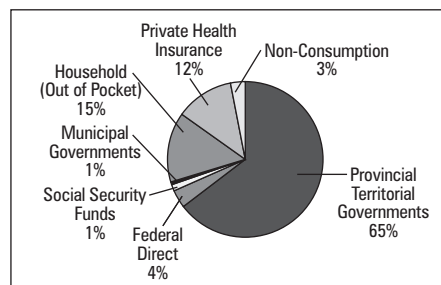


Figure 3. Canadian Health Care Dollars by Source of Funds, 2007

Source: Canadian Institute for Health Information, *National Health Expenditure Trends, 1975 to 2009*

Role of the Provincial Licensing Authorities

- the medical profession in Canada self-regulates under the authority of provincial legislation; Canada is the only country in the world where the medical profession still regulates itself
- physicians in each province are self-regulated by a licensing authority (see *Role of Professional Associations*); membership is **mandatory** to practice in that province
- system of self-regulation is based on the premise that the licensing authority must act first and foremost in the interest of the public
- Licensing Authority functions include
 - issuing non-transferable licenses allow doctors to practice only in that province
 - maintaining ethical, legal, and competency standards and developing policies to guide doctors
 - investigating complaints against doctors
 - disciplining doctors guilty of professional misconduct or incompetence (in most Canadian jurisdictions there is zero tolerance for sexual misconduct by physicians, resulting in harsh penalties including permanent suspension from the profession)

Distinction Between Licensure and Certification

- provincial licensing authorities provide non-transferable licensure to physicians
- the *Medical Council of Canada* (MCC) certifies physicians
 - certification is known as the Licentiate of the MCC (LMCC)
 - LMCC is acquired by passing the MCC Qualifying Examination Parts I and II
- the *Royal College of Physicians and Surgeons of Canada* (RCPSC) certifies specialists who complete an accredited residency program and pass the appropriate exam
 - voluntary membership of RCPSC is designated FRCPC or FRCSC (Fellow of the Royal College of Physicians/Surgeons of Canada)
- the *College of Family Physicians of Canada* (CFPC) certifies family physicians who complete an accredited residency program and pass the Certification Examination in Family Medicine
- the RCPSC and CFPC are responsible for monitoring ongoing continuing medical education (CME) and professional development



Certification by the LMCC plus either the RCPSC or CFPC is a minimum requirement for licensure by most provincial licensing authorities.

Role of Professional Associations

- provincial medical associations represent the economic and professional interests of doctors; membership is voluntary, although fee payment is mandatory in some provinces
- the *Canadian Medical Association* (CMA) is a national association that provides leadership to doctors and advocates for access to high quality health care in Canada; membership is voluntary and requires provincial medical association membership
- the CMA represents physicians' concerns at the national level, while the provincial medical associations negotiate fee and benefit schedules with provincial governments
- medical residents are represented nationally by the *Canadian Association of Interns and Residents*, and provincially by *Provincial Housestaff Organizations*, which uphold the economic and professional interests of residents
- medical students are represented at their universities by student societies; these bodies collectively form the *Canadian Federation of Medical Students*; francophone medical schools participate in the *Federation of Quebec Medical Student Societies*
- the *Canadian Medical Protective Association* (CMPA), a physician-run organization, is a voluntary insurance association that protects the integrity of member physicians by providing legal defense against allegations of malpractice or negligence and by providing risk management and educational programs, and general advice

The US Health Care System

- the United States health care system is market-based
- it is funded and delivered by a mixture of the public, private, and voluntary sectors; private-for-profit is the prevailing method of delivery
- public funding is derived from taxes raised at both the federal and state government levels

Health Care Expenditure and Delivery in the US

- health care spending in the US represents a large economic sector
 - health care comprises over 15% of the gross domestic product (GDP) (highest in the OECD), amounting to \$6714 USD per capita in 2006
 - one advantage is the widespread availability of technology – the US has 4 times as many MRI machines per capita than Canada
- the US scores poorly on some indicators of population health, with a life expectancy below the OECD average and infant mortality above the OECD average. Possible factors that account for this discrepancy are:
 - poor health of large uninsured population
 - high cost of health care administration
 - the provision of inefficient high-cost, high-intensity care
 - the higher-spending regions in the US do not provide any better quality of care, access to care, health outcomes or satisfaction with care when compared to the lower-spending regions
- the US has the highest level of obesity of all OECD nations at 34.3%; this has major implications for future health care spending

Cost of Health Care Administration in the United States and Canada

NEJM 2003; 349:768-75

Administrative costs were estimated from data on insurance overhead, employers' costs to manage benefits, and the administrative costs of hospitals, practitioners' offices, nursing homes, and home care. In 1999, the cost of U.S. health administration was \$1,059 per capita, more than three times greater than the cost in Canada (\$307 per capita).

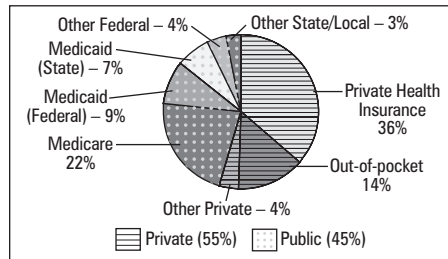


Figure 4. Personal Health Care Expenditure in USA by Source of Funds, 2007

Source: National Center for Health Statistics. *Health, United States, 2009: With Special Feature on Medical Technology*. Hyattsville, MD. 2010.

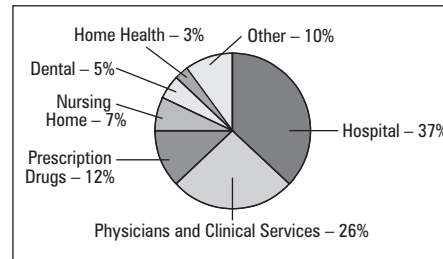


Figure 5. Personal Health Care Expenditure in USA by Type, 2007

Source: National Center for Health Statistics. *Health, United States, 2009: With Special Feature on Medical Technology*. Hyattsville, MD. 2010.

Access to Health Services

- 70% of Americans under the age of 65 have private health insurance, either employer-sponsored or individually purchased; 12% receive health care through public health insurance; 18%, mainly the poor, have no health insurance
- access to publicly funded health services occurs primarily through two programs, Medicare and Medicaid (see Table 3), which were created by the 1965 *Social Security Act*
- other federal government-funded health programs include the Military Health Services System, the Veterans Affairs Health Services System, the Indian Health Service, and the Prison Health Service

Table 3. Medicare and Medicaid Program Information

	Medicare	Medicaid
Eligibility	People over the age of 65 People with end stage renal disease People of any age meeting the Medicare definition of disability	People who receive funds through social assistance programs Pregnant women People with developmental disabilities Low-income children through the 1997 State Children's Health Insurance Program
Coverage	Basic "Part A" providing inpatient hospital care, home care, limited skilled nursing facility care, and hospice care Supplemental "Part B" covers outpatient physician and clinic services, and requires payment of a further monthly fee	Basic coverage involves inpatient and outpatient hospital care, laboratory and x-ray services, skilled nursing care, home care, physician services, dental services, and family planning Financing for Medicaid is provided jointly by the federal and state governments, and program details vary greatly between states
Co-payment	To help pay for out-of-pocket expenditures, and to cover many of the services not insured by Medicare, the majority of Medicare beneficiaries buy supplemental private health insurance	States may impose deductibles, coinsurance, or co-payments on some Medicaid recipients for certain services Medicaid is not health insurance – coverage is unreliable as improvement in an individual's financial status can lead to a loss of Medicaid eligibility

Source: Centers for Medicare and Medicaid Services; www.cms.gov

Health Care Reform

- *Patient Protection and Affordable Care Act* and the *Health Care and Education Reconciliation Act of 2010* are federal statutes signed into law in March 2010 that include a number of new healthcare provisions to be implemented over 8 years
 - expand Medicaid eligibility, provide subsidies for insurance premiums and incentives for businesses to provide health care benefits, prohibit denial of coverage/claims for pre-existing conditions, and establish health-insurance exchanges
 - costs are offset by a number of health care related taxes, including a tax penalty for citizens with no health insurance (low income persons are exempt)

Physician Responsibilities Regarding Death

- physicians are required by law to complete a medical certificate of death unless the coroner needs notification (see *Role of the Coroner*); failure to report death is a criminal offence

Role of the Coroner



Notify Coroner if Death Occurs due to:

- Violence, negligence, misconduct
- Pregnancy
- Sudden or unexpected causes
- Disease **NOT** treated
- Cause other than disease
- Suspicious circumstances

- *Coroner's Act* (specific to Ontario, similar in other provinces) requires physicians to notify a coroner or police officer if death occurs:
 - due to violence, negligence, misconduct, misadventure, or malpractice
 - during pregnancy or is attributable to pregnancy
 - suddenly and unexpectedly
 - from disease which was not treated by a legally qualified medical practitioner
 - from any cause other than disease
 - under suspicious circumstances
- coroner investigates these deaths, as well as deaths that occur in psychiatric institutions, jails, foster homes, nursing homes, hospitals to which a person was transferred from a facility, institution or home, etc.
- in consultation with forensic pathologists and other specialists, the coroner establishes:
 - the identity of the deceased
 - where and when the death occurred
 - the medical cause of death
 - the means of death (i.e. natural, accidental, suicide, homicide or undetermined)
- coroners do not make decisions regarding criminality or legal responsibility

Palliative and End-of-Life Care

- focus of care is comfort and respect for person nearing death and maximizing quality of life for patient, family, loved ones
- appropriate for any patient at any stage of a life-threatening illness
- may occur in a hospital, hospice, in the community or at home
- often an interdisciplinary team of caregivers
- addresses the medical, psychosocial, and spiritual dimensions of care

References

- Baile WF, Buckman R, Lenzi R, et al. (2000). SPIKES - A six-step protocol for delivering bad news: application to the patient with cancer. *Oncologist*. 5(4): 302-11.
- Baker GR, Norton PG, Flintoft V, Blais R, Brown A, Cox J, Etchells E, Ghali WA, Hebert P, Majumdar SR, O'Beirne M, Palacios-Derflinger L, Reid RJ, Sheps S, Tamblyn R. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. *CMAJ* 2004;170(11):1678-86.
- Canadian Institute for Health Information, National Health Expenditure Trends, 1975 to 2009 (Ottawa, Ont.: CIHI, 2009).
- Canadian Medical Association Journal "Bioethics for Clinicians" Series.
- Canadian Medical Association www.cma.ca.
- Canadian Public Health Association and WHO. Ottawa Charter for Health Promotion. Ottawa: Health and Welfare Canada, 1986.
- CMA Code of Ethics, Canadian Medical Association www.cma.ca.
- Centers for Medicare and Medicaid Services www.cms.hhs.gov.
- College of Physicians and Surgeons of Ontario www.cpso.on.ca.
- CPSO Policy Statements, College of Physicians and Surgeons of Ontario www.cpso.on.ca/policies/mandatory.htm.
- Democratic Policy Committee. Patient Protection and Affordable Care Act. http://dpc.senate.gov/dpcdoc-sen_health_care_bill.cfm
- Devereaux PJ, Choi PT, Lacchetti C, Weaver B, Schunemann HJ, Haines T, Lavis JN, Grant BJ, Haslam DR, Bhandari M, Sullivan T, Cook DJ, Walter SD, Meade M, Khan H, Bhatnagar N, Guyatt GH. A systematic review and meta-analysis of studies comparing mortality rates of private for-profit and private not-for-profit hospitals. *CMAJ* 2002;166(11):1399-406.
- Devereaux PJ, Heels-Ansell D, Lacchetti C, Haines T, Burns KE, Cook DJ, Ravindran N, Walter SD, McDonald H, Stone SB, Patel R, Bhandari M, Schunemann HJ, Choi PT, Bayoumi AM, Lavis JN, Sullivan T, Stoddart G, Guyatt GH. Payments for care at private for-profit and private not-for-profit hospitals: a systematic review and meta-analysis. *CMAJ* 2004;170(12):1817-24.
- Etchells E, Sharpe G, Elliott C and Singer PA. Bioethics for clinicians: 3. Capacity. *CMAJ* 1996;155(6):657-661.
- Ferris LE, Barkun H, Carlisle J, Hoffman B, Katz C, and Silverman M. Defining the physician's duty to warn: consensus statement of Ontario's Medical Expert Panel on Duty to Inform. *CMAJ* 1998;158:1473-1479.
- Fisher ES, Wennberg DE, Stukel TA, Gottlieb DJ, Lucas FL, Pinder EL. The implications of regional variations in Medicare spending. Part 1: the content, quality, and accessibility of care. *Ann Intern Med* 2003;138:273-87.
- Fisher ES, Wennberg DE, Stukel TA, Gottlieb DJ, Lucas FL, Pinder EL. The implications of regional variations in Medicare spending. Part 2: health outcomes and satisfaction with care. *Ann Intern Med* 2003;138:288-98.
- Government of Canada: Interagency Advisory Panel on Research Ethics www.pre.ethics.gc.ca/english/index.cfm.
- Health Care Consent Act, 1996. S.O. 1996, c. 2, Sched. A.
- Health Protection and Promotion Act, R.S.O. 1990., c.H.7; O. Reg. 559/91, amended to O. Reg. 96/03.
- Hebert P. Doing Right: A Practical Guide to Ethics for Physicians and Medical Trainees, Toronto, Oxford University Press; 1996.
- Hebert PC, Hoffmaster B, Glass KC, Singer PA. Bioethics for clinicians: 7. Truth telling. *CMAJ* 1997;156:225-8.
- Institute of Medicine. Care Without Coverage: Too Little, Too Late. Washington D.C., The National Academies Press; 2002. Online (www.iom.edu)
- Kirby, M. The Kirby Commission: The Health of Canadians – The Federal Role. 2002. Online at the Senate Canada website: <http://www.parl.gc.ca/37/2/paribus/commbus/senate/Com-e/soci-e/rep-e/repoct02vol6-e.htm>.
- Medical Council of Canada. Objectives of the considerations of the legal, ethical and organizational aspects of the practice of medicine. 1999. Online at the Medical Council of Canada website (www.mcc.ca).
- National Center for Health Statistics, Center for Disease Control and Prevention website (www.cdc.gov/nchs).
- National Center for Health Statistics. Health, United States, 2009: With Special Feature on Medical Technology. Hyattsville, MD. 2010.
- Naylor CD. Health care in Canada: incrementalism under fiscal duress. *Health Affairs* 1999;18:9-26.
- OECD. Health Data, 2008. www.oecd.org.
- Ontario Medical Association www.oma.org.
- Ontario's Office of the Chief Coroner www.mpss.jus.gov.on.ca.
- Physician Privacy Toolkit (2004), Ontario Medical Association www.oma.org/phealth/privacymain.htm.
- Romanow, R. The Romanow Report: Royal Commission on the Future of Health Care in Canada. 2002. Online at the Senate Canada website: http://www.hc-sc.gc.ca/hcs-sss/alt_formats/hpb-dgps/pdf/hhr/romanow-eng.pdf.
- Shah CP. Public health and preventive medicine in Canada. 5th ed. Toronto: Elsevier Canada; 2003. p 357-360, 426. Reprinted by permission of Elsevier Canada, 2006.
- WHO. World Health Report 2005. <http://www.who.int/whr/en>.
- Woolhandler S, Campbell T, Himmelstein DU. Costs of Health Care Administration in the United States and Canada. *NEJM* 2003; 349:768-75.

Notes_____

Alexander Huang, Lindsay MacKenzie and Pamela Lau, chapter editors

Alaina Garbens and Modupe Oyewumi, associate editors

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Anesthesia Basics

6 A's of General Anesthesia

1. Anesthesia
2. Anxiolysis
3. Amnesia
4. Areflexia (muscle relaxation not always required)
5. Autonomic Stability
6. Analgesia

Types of Anesthesia

- **general**
 - general anesthesia
 - total IV anesthesia (TIVA)
- **regional**
 - spinal, epidural
 - peripheral nerve block
 - IV regional
- **local**
 - local infiltration
 - topical
- **sedation**
 - monitored anesthesia care
- note that different types of anesthesia can be combined (e.g. general + regional)

Pre-Operative Assessment

- to identify the patient's medical and surgical issues; to allow for the arrangement of further investigations, consultations and treatments for patients not yet optimized; and to plan anesthetic techniques

History and Physical

History

- indication for surgery
- surgical/anesthetic Hx: previous anesthetics/complications, previous intubations, medications, drug allergies
- PMHx
 - CNS: seizures, stroke, raised intracranial pressure (ICP), spinal disease
 - CVS: coronary artery disease (CAD), myocardial infarction (MI), congestive heart failure (CHF), hypertension (HTN), valvular disease, dysrhythmias, peripheral vascular disease (PVD), conditions requiring endocarditis prophylaxis, exercise tolerance, CCS class, NYHA class (see Cardiology and Cardiovascular Surgery, C33 for NYHA classification)
 - respiratory: smoking, asthma, chronic obstructive pulmonary disease (COPD), recent upper respiratory tract infection (URTI), sleep apnea
 - GI: gastroesophageal reflux disease (GERD), liver disease
 - renal: insufficiency, dialysis, CKD
 - hematologic: anemia, coagulopathies, blood dyscrasias
 - MSK: conditions associated with difficult intubations – arthritides (e.g. rheumatoid arthritis), cervical tumours, cervical infections/abscess, trauma to cervical spine, Down syndrome, scleroderma, obesity, conditions affecting neuromuscular junction (e.g. myasthenia gravis)
 - endocrine: diabetes, thyroid, adrenal disorders
 - other: morbid obesity, pregnancy, ethanol/other drug use
- FHx: malignant hyperthermia, atypical cholinesterase (pseudocholinesterase), other abnormal drug/anesthetic reactions

Physical Examination

- oropharynx and airway assessment to determine the likelihood of difficult intubation
- ability to assume “sniffing position” – upper cervical spine extension, lower cervical spine flexion (assesses likelihood of difficult intubation)
- no single test is specific or sensitive – all aid in determining the ease of intubation
 - Mallampati Classification (Figure 1)
 - thyromental distance (the distance of the lower mandible in the midline from the mentum to the thyroid notch)
 - ♦ with the adult patient's neck fully extended, <3 finger breadths (<6 cm) is associated with difficult intubation

- mouth opening (<2 finger breadths is associated with difficult intubation)
- tongue size
- dentition, dental appliances/prosthetic caps – must inform patients of the rare possibility of damage
- nasal passage patency (if planning nasotracheal intubation)
- bony landmarks and suitability of anatomy for regional anesthesia (if relevant)
- focused physical exam of the CNS, CVS, and respiratory systems
- general assessment of nutrition, hydration, and mental status
- pre-existing motor and sensory deficits
- sites for IV, central venous pressure (CVP), and pulmonary artery (PA) catheters

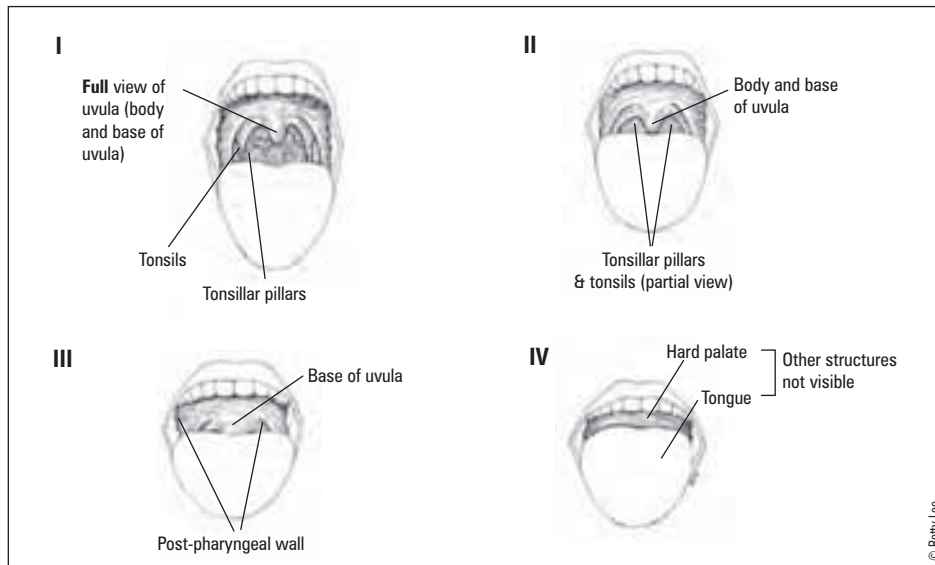


Figure 1. Mallampati Classification of Upper Airway Visualization

Pre-Operative Investigations

Table 1. Suggested Indications for Specific Investigations in the Pre-Operative Period

Test	Indications
CBC	Major surgery requiring group and screen or cross and match; chronic cardiovascular, pulmonary, renal, or hepatic disease; malignancy; known or suspected anemia; bleeding diathesis or myelosuppression in patient less than 1 year of age
Sickle cell screen	Genetically predisposed patient (hemoglobin electrophoresis if screen is positive)
INR, aPTT	Anticoagulant therapy, bleeding diathesis, liver disease
Electrolytes and Creatinine	Hypertension, renal disease, diabetes, pituitary or adrenal disease; digoxin or diuretic therapy, or other drug therapies affecting electrolytes; age >50
Fasting glucose level	Diabetes (repeat on day of surgery)
Pregnancy (beta-HCG)	Women of childbearing age
ECG	Heart disease, hypertension, diabetes, other cardiac risk factors (may include age), subarachnoid hemorrhage, CVA, head trauma, age (male >40 y.o., female >50 y.o.)
Echocardiogram	CHF, cardiomyopathy, valvular pathology, limited cardiac reserve, stroke of unknown etiology
Chest radiograph	Cardiac or pulmonary disease, malignancy, age >60

Guidelines to the Practice of Anesthesia, Revised 2006. Supplement to the Canadian Journal of Anesthesia, Vol 53(12), Dec. 2006. Reproduced with permission © Canadian Anesthesiologists' Society.

Fasting Guidelines

Fasting Guidelines Prior to Surgery (Canadian Anesthesiologists' Society)

- **8 hours** after a meal that includes meat, fried or fatty foods
- **6 hours** after a light meal (such as toast, crackers and clear fluid) or after ingestion of infant formula or nonhuman milk
- **4 hours** after ingestion of breast milk or jello
- **2 hours** after clear fluids (water, black coffee, tea, carbonated beverages, juice without pulp)

Impact of Anesthesia Management Characteristics on Severe Morbidity and Mortality

Anesthesiology 2005; 102(2):257-258

Study: Case-control study of patients undergoing anesthesia.

Patients: 803 cases and 883 controls were analyzed among a cohort of 869,483 patients undergoing anesthesia between 1995-1997. Cases were defined as patients who either remained comatose or died within 24 hours of receiving anesthesia. Controls were defined as patients who neither remained comatose nor died within 24 hours of receiving anesthesia.

Intervention: General, regional, or combined anesthesia to patients undergoing a surgical procedure.

Main Outcome: coma or death within 24 hours of receiving anesthesia

Results: The incidence of 24-hour postoperative death was 8.8 per 10,000 anesthetics (95% CI, 8.2-9.5) and the incidence of coma was 0.5 (95% CI, 0.3-0.6). Anesthesia management risk factors that were associated with a decreased risk of morbidity and mortality were: equipment check with protocol and documentation, directly available anesthesiologist with no change during anesthesia, 2 persons present at emergence of anesthesia, reversal of muscle relaxation, and postoperative pain medication.

American Society of Anesthesiology (ASA) Classification

- common classification of physical status at the time of surgery
- a gross predictor of overall outcome, NOT used as stratification for anesthetic risk (mortality rates)
- **ASA 1:** a healthy, fit patient
- **ASA 2:** a patient with mild systemic disease, e.g. controlled Type 2 diabetes, controlled essential HTN, obesity, smoker
- **ASA 3:** a patient with severe systemic disease that limits activity, e.g. stable CAD, COPD, DM, obesity
- **ASA 4:** a patient with incapacitating disease that is a constant threat to life, e.g. unstable CAD, renal failure, acute respiratory failure
- **ASA 5:** a moribund patient not expected to survive 24 hours without surgery, e.g. ruptured abdominal aortic aneurysm (AAA), head trauma with increased ICP
- for emergency operations, add the letter E after classification (e.g. ASA 3E)

Pre-Operative Optimization

- in general, any fluid and/or electrolyte imbalance should be corrected prior to elective surgery

Medications

- pay particular attention to cardiac and respiratory meds, narcotics and drugs with many side effects and interactions
- **pre-operative medications to start**
- prophylaxis
 - risk of GE reflux: sodium citrate 30 mL PO or ranitidine 150-300 mg PO 30 min to 1 hour pre-op
 - risk of infective endocarditis, GI/GU interventions: antibiotics
 - risk of adrenal suppression: steroid coverage
 - risk of DVT: heparin SC
 - consider oral benzodiazepines for the anxious patient
- optimization of co-existing disease: bronchodilators (COPD, asthma), nitroglycerin and beta-blockers (CAD risk factors)
- **pre-operative medications to stop**
 - oral hypoglycemics: stop on morning of surgery
 - antidepressants (tricyclics, MAOIs): stop on morning of surgery
- **pre-operative medication to adjust**
 - insulin, prednisone, coumadin, bronchodilators

Hypertension

- mild to moderate HTN is not an independent risk factor for peri-operative cardiovascular complications (*Lette et al. Ann. Surg.* 1992; 216:192-204)
- target sBP <180 mmHg, dBP <110 mmHg
- assess for absence/presence of end-organ damage and treat accordingly

Coronary Artery Disease (CAD)

- ACC/AHA Guidelines (2007) recommend postponing elective surgery 4-6 weeks following an MI
- this period carries an increased risk of reinfarction/death
 - <3 months after MI – 37% patients may reinfarct
 - 3-6 months after MI – 15%
 - >6 months after MI – risk remains constant at 5%
- if operative procedure is essential, and cannot be delayed, invasive intra and post-operative ICU monitoring reduces the risk to 6%, 2% and 1% respectively for the above time periods
- mortality with peri-operative MI is 20-50%
- initiation of peri-operative beta-blockade in patients with increased risk of CVA
 - beta-blockade should be continued if already started
 - initiate beta-blockade if inducible ischemia, CAD or multiple cardiac risk factors and undergoing high risk surgery
 - consider initiating beta-blockade if CAD or multiple cardiac risk factors and undergoing intermediate risk surgery
 - treatment with beta-blockers should be optimized well in advance of any surgery



Risk Assessment

1. Reconcile patient factors with surgical needs and devise a safe and effective anesthetic plan
2. Optimize co-morbidities

Effects of Extended-release Metoprolol Succinate in Patients Undergoing Non-Cardiac Surgery (POISE trial): A Randomised Controlled Trial.

Lancet 2008; 371:1839-47

Purpose: To investigate the role of beta-blockers (metoprolol) peri-operatively in patients with known vascular disease, undergoing non-cardiac surgery.

Methods: Patients from 190 centres in 23 countries were eligible if they were >45, undergoing non-cardiac surgery and were known to have significant vascular disease. Patients were randomised to either the metoprolol group or placebo. Participants received metoprolol (or placebo) 100 mg 2.4 hours before surgery and again 6 hours after surgery and following that 200 mg daily for 30 days. The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal cardiac arrest. Analyses was by intention to treat.

Results: 8351 patients were recruited into the study, with 8331 completing the 30 day course. Use of metoprolol was found to significantly reduce the risk of cardiovascular death, non-fatal MI or non-fatal cardiac arrest vs. placebo (hazard ratio 0.84, $p < 0.05$) but significantly increased the rate of stroke (hazard ratio 2.17, $p < 0.01$) and overall risk of death (hazard ratio 1.33, $P < 0.05$).

Conclusion: Use of peri-operative beta-blockers (metoprolol) in patients with known vascular disease provides both risks and benefits, and these must be considered for each patient individually.

Endocrine Disorders

- diabetes mellitus
 - hypoglycemia
 - ♦ caused by drugs and surgical stresses and masked by anesthesia
 - ♦ prevent with dextrose/insulin infusion and blood glucose monitoring
 - end organ damage: be aware of damage to CVS, renal and nervous systems, including autonomic neuropathy
- hyperthyroidism
 - can experience sudden release of thyroid hormone (thyroid storm)
 - treatment: beta-blockers + pre-op prophylaxis
- adrenocortical insufficiency e.g. Addison's, exogenous steroid use
 - steroid coverage suggested if steroid use of >1 week in past 6 months

Respiratory Diseases

- asthma
 - bronchospasm from intubation, delivery of inhaled anesthetics
 - pre-op inhaled salbutamol may mitigate risk
 - avoid non-selective beta-blockers, caution with beta2 specific
 - cancel/delay elective surgery for poorly controlled asthma
- smoking
 - adverse effects: altered mucus secretion and clearance, decreased small airway caliber and altered immune response
 - abstain at least 8 weeks pre-op, if possible
 - if unable, abstaining even 24 hours pre-op has shown benefit
- COPD
 - anesthesia, surgery and analgesia predispose to atelectasis, bronchospasm, pneumonia, prolonged mechanical ventilation and respiratory failure
 - cancel/delay elective surgery for acute exacerbation
 - optimize with bronchodilators ± inhaled corticosteroids ± antibiotics

Aspiration

- risk of aspiration in gastroesophageal (GE) sphincter incompetency, GERD or hiatus hernia
- avoid inhibiting airway reflexes; reduce gastric volume and acidity
- employ rapid sequence induction if increased risk (see RSI, A9)
- increased risk with laryngeal mask (instead of ETT)

Monitoring

Canadian Guidelines to the Practice of Anesthesia and Patient Monitoring

- an anesthetist present: "the only indispensable monitor"
- a completed pre-anesthetic checklist: including ASA class, NPO policy, Hx and investigations
- a peri-operative anesthetic record: HR and BP q5min, dose and route of drugs and fluids
- continuous monitoring:
 - oxygenation
 - ventilation
 - circulation
 - temperature

Routine Monitors for All Cases

- **BP cuff, telemetry, pulse oximeter** (O₂ saturation), stethoscope, temperature probe, gas analyzer, capnometer (end tidal CO₂ to assess adequacy of ventilation)

Elements to Monitor (Figure 2)

- anesthetic depth
 - inadequate: blink reflex present when eyelashes lightly touched, HTN, tachycardia, tearing or sweating
 - excessive: hypotension, bradycardia
- oxygenation: pulse oximetry, inspired O₂ concentration (FiO₂)
- ventilation: verification of correctly positioned ETT, chest excursions, breath sounds, end tidal CO₂ analysis, end tidal inhaled anesthesia analysis
- circulation: pulse, heart sounds, BP, telemetry, oximetry, central venous pressure (CVP), pulmonary capillary wedge pressure
- temperature: temperature probe



Pre-Anesthetic Checklist

SAMMM

Suction – connected and working
Airways – laryngoscope and blades, ETT, syringe, stylet, oral and nasal airways, tape, bag and mask
Machine – connected, pressures okay, all meters functioning, vaporizers full
Monitors – available, connected and working
Medications – IV fluids and kit ready, emergency medicines in correct location and accessible

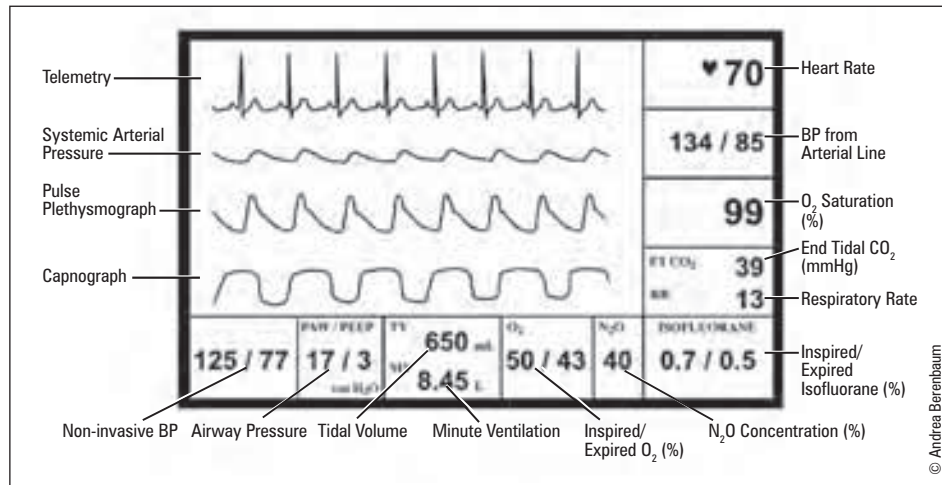


Figure 2. Typical Anesthesia Monitor

Induction Agents

- induction may be achieved with intravenous agents, volatile agents or both

Intravenous Agents

- Table 11, A25
- the IV induction agents include a selection of non-opioid drugs used to provide amnesia and blunt reflexes. These are initially used to draw the patient into the maintenance phase of general anesthesia rapidly, smoothly, and with little adverse effects
 - e.g. propofol, sodium thiopental or ketamine
 - propofol and ketamine are also used for the maintenance phase of GA

Volatile Inhalational Agents

- Table 13, A26
- general concepts of volatile agents are discussed below
 - e.g. sevoflurane, desflurane, isoflurane, enflurane, halothane and nitrous oxide

MAC (minimum alveolar concentration)

- definition: the alveolar concentration of an agent at one atmosphere (atm) of pressure that will prevent movement in 50% of patients in response to a surgical stimulus (e.g. abdominal incision)
- often 1.2-1.3 times MAC will ablate response in the general population
- potency of inhalational agents is compared using MAC
- MAC values are roughly additive when mixing N₂O with another volatile agent (i.e. 0.5 MAC of a potent agent + 0.5 MAC of N₂O = 1 MAC of potent agent; however, this only applies to movement, not other effects such as blood pressure changes and does not hold over the entire N₂O dose range)
- MAC-intubation: the MAC of anesthetic that will inhibit movement and coughing during endotracheal intubation, generally 1.3 MAC
- MAC-block adrenergic response (MAC-BAR): the MAC necessary to blunt the sympathetic response to noxious stimuli, generally 1.5 MAC
- MAC-awake: the MAC of a given volatile anesthetic at which a patient will open their eyes to command, usually 0.3-0.4 of the usual MAC value



Determinants of Speed of Onset of Volatile Anesthetics

- Solubility:** decrease solubility, increase rate of induction
- Cardiac Output (CO):** as CO increases, anesthetic uptake to blood increases and alveolar gas concentration decreases, thus delaying induction
- Partial pressure difference between alveolar and venous blood:** increase gradient, decrease rate of induction
- Inspired Gas Concentration:** increase inspired concentration, increase rate of induction
- Alveolar Ventilation:** increase alveolar ventilation, increase rate of induction
- Second Gas Effect:** when 2 gases are administered together, uptake of the first gas (e.g. N₂O) increases the alveolar concentration of the second gas (e.g. desflurane), increase rate of induction



Solubility of Volatile Anesthetics in Blood Least soluble → Most soluble

Nitrous oxide < desflurane < sevoflurane < isoflurane < halothane

Muscle Relaxants and Reversing Agents

- depolarizing muscle relaxants: succinylcholine (SCh)
- non-depolarizing: rocuronium, mivacurium, vecuronium
- specific muscle relaxants are described in Tables 14 and 15

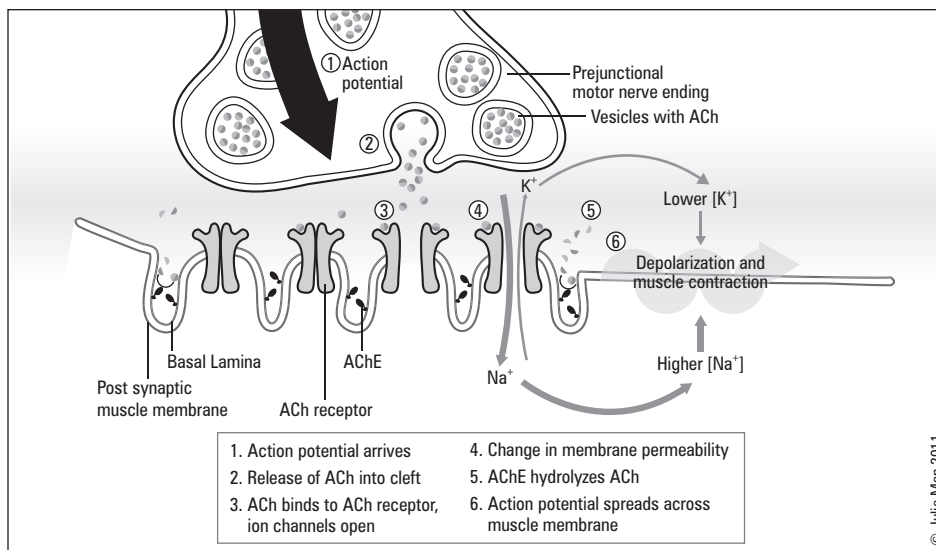


Figure 3. Anatomy and Physiology of the Neuromuscular Junction (NMJ)

Muscle Relaxants

- muscle relaxation produces the following desired effects:
 1. facilitates intubation
 2. assists with mechanical ventilation
 3. prevents muscle stretch reflex and decreases muscle tone
 4. allows access to the surgical field (intracavitary surgery)
- never use without adequate preparation and equipment to maintain airway and ventilation
- blocks nicotinic cholinergic receptors in NMJ
- provides skeletal muscle paralysis, including the diaphragm, but spares involuntary muscles such as the heart and smooth muscle
- nerve stimulator is used intraoperatively to assess the degree of nerve block; no twitch response seen with complete neuromuscular blockade

Reversing Agents for Non-Depolarizing Muscle Relaxants (e.g. neostigmine, pyridostigmine, edrophonium)

- reversal agents are acetylcholinesterase inhibitors
 - inhibits enzymatic degradation of ACh; increases amount of ACh at nicotinic and muscarinic receptors, displacing non-depolarizing muscle relaxant
- anticholinergic agents, such as atropine or glycopyrrolate, are simultaneously administered to minimize muscarinic effect of reversal agents (i.e. bradycardia, salivation and increased bowel peristalsis)



Plasma Cholinesterase

Plasma cholinesterase is produced by the liver and metabolizes SCh, ester local anesthetics, and mivacurium. A prolonged duration of blockade by SCh occurs with:

- (a) decreased quantity of plasma cholinesterase, e.g. liver disease, pregnancy, malignancy, malnutrition, collagen vascular disease, hypothyroidism.
- (b) abnormal quality of plasma cholinesterase, i.e. normal levels but impaired activity of enzymes, genetically inherited.

Airway Management

Airway Anatomy Review

- normal airway: nares → nasal cavities → nasal pharynx → laryngeal pharynx → trachea
- resistance to airflow through nasal passages accounts for approximately 2/3 of total airway resistance
- pharyngeal airway extends from posterior aspect of the nose to cricoid cartilage
- the glottic opening (triangular space formed between the true vocal cords) is the narrowest segment of the laryngeal opening in adults
- when intubating, the glottic opening is used as the space through which one visualizes proper placement of the endotracheal tube (ETT)
- the trachea begins at the level of the thyroid cartilage at the level of C6
- the trachea bifurcates into the right and left main bronchi at the level of T5

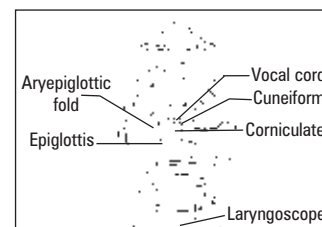


Figure 4. Landmarks for Intubation

Table 2. Methods of Supporting the Airway

	Bag and Mask	Laryngeal Mask Airway (LMA)	Endotracheal Tube (ETT)
Advantages/Indications	<ul style="list-style-type: none"> • Basic • Non-invasive • Readily available 	<ul style="list-style-type: none"> • Easy to insert • Less airway trauma/irritation than ETT • Frees up hands (vs. face mask) • Primarily used in spontaneously ventilating patient 	<p>"The 5 P's"</p> <ul style="list-style-type: none"> • Ensures airway Patency • Protects against aspiration • Allows Positive pressure ventilation • Allows suctioning i.e. "Pulmonary toilet" • A route for Pharmacological administration
Disadvantages/Contraindications	<ul style="list-style-type: none"> • Risk of aspiration if ↓ LOC • Cannot ensure airway patency • Inability to deliver precise tidal volume • Operator fatigue 	<ul style="list-style-type: none"> • Risk of gastric aspiration • PPV > 20 cm H₂O needed • Limited TMJ mobility • C-spine or laryngeal cartilage fracture • Oropharyngeal, retropharyngeal pathology or foreign body 	<ul style="list-style-type: none"> • Insertion can be difficult • Muscle relaxant usually needed • Laryngospasm may occur on failed intubation or extubation • Sympathetic stress due to intubation
Other	<ul style="list-style-type: none"> • Facilitate airway patency with jaw thrust and chin lift • Can use oropharyngeal/nasopharyngeal airway 	<ul style="list-style-type: none"> • Does NOT protect against laryngospasm or gastric aspiration • Sizing (approx): 40-50 kg: 3 50-70 kg: 4 70-100 kg: 5 	<ul style="list-style-type: none"> • Auscultate to avoid endobronchial intubation • Sizing (approx): Male: 8.0-9.0 mm Female: 7.0-8.0 mm Pediatric: (age/4) + 4 mm



Tracheal Intubation

Equipment for Intubation

- oxygen source and self-inflating bag
- face mask (appropriate size and one size larger and smaller)
- oropharyngeal and nasopharyngeal airways
- endotracheal tubes (appropriate size and one size smaller)
- tracheal stylet
- syringe for tube cuff inflation
- suction
- laryngoscopes

Preparing for Intubation

- failed attempts at intubation can make further attempts more difficult due to tissue trauma
- plan, prepare and assess for potential difficulties (see *Pre-operative Assessment*, A2)
- ensure equipment is available and working (e.g. test ETT cuff, check laryngoscope light, machine check)
- pre-oxygenate/denitrogenate: patient breathes 100% O₂ for 3-5 min or for 4 vital capacity breaths
- may need to suction mouth and pharynx first

Proper Positioning for Intubation

- "sniffing position": flexion of lower C-spine (C5,6), i.e. bow head forward and extension of upper C-spine at atlanto (C1)-occipital joint, i.e. nose in the air
- aligns the three axes of mouth, pharynx and larynx to allow visualization from the oral cavity to the glottis (Figure 5)
- proper position for laryngoscope tip to visualize cords is in the epiglottic vallecula
- contraindicated in known/suspected C-spine fracture/instability

Tube Insertion

- ETT insertion can incite a significant sympathetic response due to a "foreign body reflex" in the trachea, including: tachycardia, dysrhythmias, myocardial ischemia, increased BP and coughing
- a malpositioned ETT is a potential hazard for the intubated patient
 - if too deep, may result in right endobronchial intubation, which is associated with left-sided atelectasis and right-sided tension pneumothorax
 - if too shallow, may lead to accidental extubation, vocal cord trauma or laryngeal paralysis as a result of pressure injury by the ETT cuff
- the tip of ETT should be located at the midpoint of the trachea at least 2 cm above the carina and the proximal end of the cuff should be placed at least 2 cm below the vocal cords
 - approximately 20-23 cm mark at the right corner of the mouth for men and 19-21 cm for women

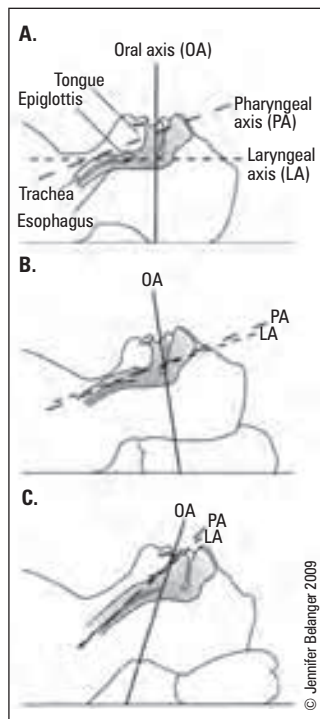


Figure 5. Anatomic Considerations in Laryngoscopy

A. neutral position, B. C-spine flexion, C. C-spine flexion with atlanto-occipital extension.

Confirmation of Tracheal Placement of ETT

- direct
 - visualization of ETT passing through cords
 - bronchoscopic visualization of ETT in trachea
- indirect
 - end-tidal CO₂ in exhaled gas measured by capnograph
 - auscultate for equal breath sounds bilaterally and absent breath sounds over epigastrium
 - chest movement and no abdominal distention
 - feel the normal compliance of lungs when ventilating patient
 - condensation of water vapour in ETT visible during exhalation
 - refilling of reservoir bag during exhalation
 - AP or lateral CXR: ETT tip at midpoint of thoracic inlet and carina (lateral CXR more sensitive and specific)

Complications During Laryngoscopy and Intubation

- mechanical
 - dental damage
 - laceration (lips, gums, tongue, pharynx, esophagus)
 - laryngeal trauma
 - esophageal or endobronchial intubation
 - accidental extubation
 - insufficient cuff inflation or cuff laceration: results in leaking and aspiration
- systemic
 - laryngospasm
 - bronchospasm
- esophageal intubation suspected when
 - end-tidal CO₂ zero or near zero on capnograph
 - abnormal sounds during assisted ventilation
 - impairment of chest excursion
 - hypoxia/cyanosis
 - presence of gastric contents in ETT
 - distention of stomach/epigastrium with ventilation



Intubation Tools

MD SOLES
Monitoring
Drugs
Suction
Oxygen
Laryngoscopes
ETT
Stylet, Syringe



Medications that can be given through the ETT

NAVEL
Naloxone
Atropine
Ventolin
Epinephrine
Lidocaine



Differential Diagnosis of Poor Bilateral Breath Sounds after Intubation

DOPE
Displaced ETT
Obstruction
Pneumothorax
Esophageal intubation

Rapid Sequence Induction (RSI)

- indicated when patient has “full stomach”, i.e. predisposed to regurgitation/aspiration:
 - decrease level of consciousness (LOC)
 - trauma
 - meal within 6 hours
 - sphincter incompetence suspected (GERD, hiatus hernia, nasogastric tube)
 - increased abdominal pressure (pregnancy, obesity, bowel obstruction, acute abdomen)
- pre-oxygenate/denitrogenate: patient breathes 100% O₂ for 3-5 minutes or for 4 vital capacity breaths prior to induction of anesthesia (do NOT bag ventilate)
- assistant performs Sellick's maneuver: pressure on cricoid cartilage to compress esophagus between cartilage and C6 to prevent reflux/aspiration
- administration of induction agent immediately followed by fast acting muscle relaxant (e.g. SCH)
- intubate shortly after administration of muscle relaxant (approximately 45-60 seconds) with no bag-mask ventilation in between induction and intubation
- must use cuffed ETT to prevent aspiration of gastric contents
- inflate cuff, verify correct placement of ETT, release cricoid cartilage pressure
- ventilate when ETT in place and cuff inflated

Difficult Airway

- difficulties with bag-mask ventilation, supraglottic airway, endotracheal intubation, infraglottic airway or surgical airway
- algorithms exist for difficult airways (e.g. *Anesthesiology* 2003; 98:3273, *Anaesthesia* 2004; 59:675)
- pre-op assessment (history of previous difficult airway, airway examination) and pre-oxygenation are important preventative measures
- if difficult airway expected, consider:
 - awake intubation
 - intubating with bronchoscope, trachlight (lighted stylet), fibre-optic laryngoscope, glidescope, etc.
- if intubation unsuccessful after induction:
 1. CALL FOR HELP
 2. ventilate with 100% O₂ via bag and mask
 3. consider returning to spontaneous ventilation and/or waking patient

Predicting Difficult Intubation in Apparently Normal Patients

Anesthesiology 2005; 103:429-37

Purpose: To assess widely available bedside tests and widely used laryngoscopic techniques in the prediction of difficult intubations.

Study: Meta-analysis.

Patients: 35 studies encompassing 50,760 patients.

Definitions: Difficult intubation was defined usually as Cormack-Lehane grade of 3 or greater, but some authors reported the requirement of a special technique, multiple unsuccessful attempts, or a combination of these as the accepted standard for difficult intubation.

Results: The overall incidence of difficult intubation was 5.8% (95% CI, 4.5–7.5%) for the overall patient population, 6.2% (95% CI, 4.6–8.3%) for normal patients excluding obstetric and obese patients, 3.1% (95% CI, 1.7–5.5%) for obstetric patients, and 15.8% (95% CI, 14.3–17.5%) for obese patients.

Mallampati score: SN: 49% SP:86% PLR:3.7 NLR:0.5, Thyromental distance: SN:20% SP:94% PLR:3.4 NLR:0.8 Sternomental distance: SN:62% SP:82% PLR:5.7 NLR:0.5, Mouth opening: SN:22% SP:97% PLR: 4.0 NLR:0.8, Wilson risk-sum: SN:46% SP:89% PLR:5.8 NLR:0.6, Combination Mallampati and thyromental distance: SN:36% SP:87% PLR:9.9 NLR:0.6

Conclusions: A combination of the Mallampati test and thyromental distance is the most accurate at predicting difficult intubation. The positive likelihood ratio (9.9) is supportive of the test as a good predictor of difficult intubation.

PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; SN: Sensitivity; SP: Specificity

- if bag and mask ventilation inadequate:
 1. CALL FOR HELP
 2. attempt ventilation with oral airway
 3. consider/attempt LMA
 4. emergency invasive airway access (e.g. rigid bronchoscope, cricothyrotomy or tracheostomy)

Intraoperative Management



Oxygen Therapy

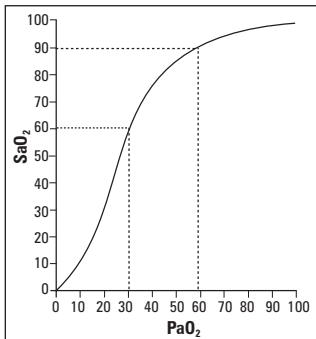


Figure 6. HbO₂ Saturation Curve

- in general the goal of oxygen therapy is to maintain oxygen saturation (SaO₂) >90%
- below an SaO₂ of 90%, a small decrease in saturation corresponds to a large drop in PaO₂ (Figure 6)
- in intubated patients, oxygen is delivered via the endotracheal tube (ETT)
- in patients not intubated, there are many oxygen delivery systems available; the choice depends on oxygen requirements (FiO₂) and the degree to which precise control of delivery is needed
- cyanosis can be detected at SaO₂ = 80%, frank cyanosis at SaO₂ = 67%

Low Flow Systems

- acceptable if tidal volume 300-700 ml, respiratory rate (RR) <25, consistent ventilation pattern
- provide O₂ at flows between 0-8 L/min
- dilution of oxygen with room air results in a decrease in the inspired oxygen concentration (FiO₂)
- an increase in minute ventilation (tidal volume x RR) results in a decrease in the inspire oxygen concentration
- e.g. **nasal canula (prong)**
 - well tolerated if flow rates <5-6 L/min, at high flows drying of nasal mucosa
 - the nasopharynx acts as an anatomic reservoir that collects O₂
 - the delivered oxygen concentration (FiO₂) can be estimated by adding 4% for every additional litre of O₂ delivered (e.g. at normal tidal volume and RR, flow rate of 1-6 L/min equate to FiO₂ of 24-44%)

Reservoir Systems

- use a volume reservoir to accumulate oxygen during exhalation thus increasing the amount of oxygen available for the next breath
- **simple face mask (Hudson face mask)**
 - covers patient's nose and mouth and provides an additional reservoir beyond nasopharynx
 - fed by small bore O₂ tubing at a rate of at least 6 L/min to ensure that exhaled CO₂ is flushed through the exhalation ports and not rebreathed
 - FiO₂ of 55% can be achieved at O₂ flow rates of 10 L/min
- **non-rebreather mask**
 - reservoir bag and a series of one-way valves direct gas flow from the bag on inhalation and allow release of expired gases on exhalation, thus allowing for oxygen accumulation during intubation
 - O₂ flow rates of 10-15 L/min are needed to maintain the reservoir bag inflation and should deliver FiO₂ >80%

High Flow Systems

- generates flows of up to 50-60 L/min
- meets/exceeds patient's inspiratory flow requirement
- delivers consistent and predictable concentration of O₂
- **Venturi mask**
 - delivers specific percentages of oxygen by varying the size of air entrainment
 - port determines the oxygen concentration (i.e. can vary to achieve 24%, 28%, 35%, 50%)
 - enables control of gas humidity
- **Puritan mask**
 - delivers the highest level of humidified oxygen

Ventilation

- in patients given muscle relaxants, ventilation is maintained with positive pressure ventilation (PPV)
- if no muscle relaxant is given patients may have sufficient spontaneous respirations to maintain ventilation, or assisted/controlled ventilation can be used



Alveolar O₂ Gas Equation

$$PAO_2 = FiO_2 (P_{atm} - P_{H_2O}) - PaCO_2$$



Arterial O₂ Content

$$CaO_2 = (SaO_2)(Hb)(1.34) + (PaO_2)(0.003)$$

CaO₂ = arterial O₂ content

SaO₂ = % hemoglobin saturation

PaO₂ = arterial O₂ pressure

- other indications of mechanical ventilation:
 - apnea
 - hypoventilation
 - intraoperative positioning limiting respiratory excursion (e.g. prone, Trendelenburg)
 - required hyperventilation (to lower intracranial pressure)
 - deliver positive end expiratory pressure (PEEP)
 - increased intrathoracic pressure (e.g. laparoscopic procedure)
- complications of mechanical ventilation:
 - decreased CO₂ due to hyperventilation
 - decreased BP due to decreased venous return from increased intrathoracic pressure
 - alkalemia with over correction of chronic hypercarbia
 - nosocomial pneumonia/bronchitis
- see Respirology, R27 for ventilatory modes

Table 3. Causes of Intraoperative Hyper- and Hypocapnea

Hypocapnea (↓ CO ₂)	Hypercapnea (↑ CO ₂)
Hyperventilation	Hypoventilation
Hypothermia	Hyperthermia
Decreased blood flow to lungs	Improved blood flow to lungs after resuscitation or hypotension
Incorrect placement of sampling catheter	Low bicarbonate
Inadequate sampling volume	Anesthetic breathing circuit error <ul style="list-style-type: none"> • Inadequate fresh gas flow • Rebreathing, faulty circuit absorber valves • Exhausted soda lime
Incipient pulmonary edema	
Air embolism	Water in capnography device

Temperature

Causes of Hypothermia (<36.0°C)

- intraoperative temperature losses are common (e.g. 90% of intraoperative heat loss is transcutaneous), due to:
 - OR environment (cold room, IV fluids, instruments)
 - open wound
- prevent with inflated warming blanket and warmed IV fluids (if giving platelet transfusion put through a line that does not go through warmer, warmer distorts viability of platelets)

Causes of Hyperthermia (>37.5-38.3°C)

- drugs (e.g. atropine)
- blood transfusion reaction
- infection/sepsis
- medical disorder (e.g. thyrotoxicosis)
- malignant hyperthermia (see *Uncommon Complications*, A24)
- over-zealous warming efforts

Heart Rate

Causes of Intraoperative Tachycardia

- confirm it is sinus tachycardia vs. other rhythms (e.g. atrial fibrillation/flutter, paroxysmal atrial tachycardia, accessory pathway syndromes, ventricular tachycardia)
- causes of sinus tachycardia:
 - shock/hypovolemia/blood loss
 - anxiety/pain/light anesthesia
 - full bladder
 - anemia
 - febrile illness/sepsis
 - drugs (e.g. atropine, cocaine, dopamine, epinephrine, ephedrine, isoflurane, isoproterenol, pancuronium)
 - Addisonian crisis, hypoglycemia, transfusion reaction, malignant hyperthermia

Causes of Intraoperative Bradycardia

- increased parasympathetic tone vs. decreased sympathetic tone
- **must** rule out hypoxemia
- arrhythmias (see Cardiology and Cardiovascular Surgery, C12)
- baroreceptor reflex due to increased intracranial pressure or increased blood pressure
- vagal reflex (occulocardiac reflex, carotid sinus reflex, airway manipulation)
- drugs (e.g. succinylcholine, opioids, edrophonium, neostigmine, halothane, digoxin, beta-blockers)
- high spinal/epidural anesthesia



Suspect difficult ventilation with:

BONES

Beard
Obesity/Obstetrics
No teeth
Elderly
Sleep apnea



Causes of Intraoperative Hypoxia

Inadequate oxygen supply: e.g. breathing system disconnection, obstructed or malpositioned ETT, leaks in the anesthetic machine, loss of oxygen supply.

Hypoventilation

Ventilation-perfusion inequalities: e.g. atelectasis, pneumonia, pulmonary edema, pneumothorax.

Reduction in oxygen carrying capacity: e.g. anemia, carbon monoxide poisoning, methemoglobinemia, hemoglobinopathy.

Leftward shift of the hemoglobin-oxygen saturation curve: e.g. hypothermia, decreased 2,3-DPG, alkalosis, hypocarbia, carbon monoxide poisoning.

Right-to-Left cardiac shunt



Hypothermia (32°-35.9°C)

Impact on Outcomes

Reduces resistance to wound infections by impairing immune function.

Increases the period of hospitalization by delaying healing.

Reduces platelet function and impairs activation of coagulation cascade increasing blood loss and transfusion requirements.

Triples the incidence of V-tach and morbid cardiac events.

Decreases the metabolism of anesthetic agents prolonging post-op recovery.



Blood Pressure



Intraoperative Shock

SHOCKED

Sepsis or Spinal shock
Hypovolemic/Hemorrhagic
Obstructive
Cardiogenic
anaphylactic
Extra/other
Drugs

Causes of Intraoperative Hypotension/Shock (sBP <90 mmHg or MAP <60 mmHg)

a) hypovolemic/hemorrhagic shock

- see Infectious Diseases, ID24
- most common form of shock, due to blood loss or dehydration
- class 1 hemorrhage: 0-15% of blood volume or <3% total body water (TBW)
 - ♦ decreased peripheral perfusion of organs able to withstand prolonged ischemia (skin, fat, muscle, bone)
 - ♦ patient feels cold, postural hypotension and tachycardia, cool/pale/moist skin, low JVP, decreased CVP, increased peripheral vascular resistance, concentrated urine
 - ♦ treatment: rapidly infuse 1-2 L of balanced salt solutions (BSS), then maintenance fluids
- class 2 hemorrhage: 15-30% of blood volume or approximately 6% of TBW
 - ♦ thirst, supine hypotension and tachycardia, oliguria or anuria
 - ♦ treatment: rapidly infuse 2 L of BSS then re-evaluate continued needs
- class 3 hemorrhage: 30-40% of blood volume
 - ♦ mildly decreased perfusion to heart and brain
 - ♦ marked tachypnea, tachycardia, decreased sBP, oliguria, confusion
 - ♦ treatment: rapidly infuse 2 L of BSS
 - ♦ replace blood losses with BSS (1:3) or PRBCs, colloid (1:1)
 - ♦ maintain urine output >0.5 mL/kg/hr
- class 4 hemorrhage: >40% of blood volume or approximately 9% of TBW
 - ♦ decreased perfusion of heart and brain
 - ♦ agitation, confusion, obtundation, supine hypotension and tachycardia, rapid deep breathing, anuria
 - ♦ treatment: same as class 3

b) obstructive shock

- obstruction of blood into or out of the heart
- increased JVP, distended neck veins, increased systemic vascular resistance, insufficient cardiac output (CO)
- e.g. tension pneumothorax, cardiac tamponade, pulmonary embolism

c) cardiogenic shock

- myocardial dysfunction
- increased JVP, distended neck veins, increased systemic vascular resistance, decreased CO
- e.g. dysrhythmias, ischemia/infarct, cardiomyopathy, acute valvular dysfunction

d) septic shock

- bacterial, viral, fungal, endotoxins/mediators cause vasodilation and capillary leakage
- associated with contamination of open wounds, intestinal injury or penetrating trauma
- fever, decreased JVP, wide pulse pressure, increased cardiac output, increased HR, decreased systemic vascular resistance \pm pressors
- initial treatment: antibiotics, volume expansion

e) spinal/neurogenic shock

- decreased sympathetic tone
- hypotension without tachycardia or peripheral vasoconstriction (warm skin)

f) anaphylactic shock

- see Emergency Medicine, ER30
- acute/subacute generalized allergic reaction due to an inappropriate or excessive immune response (type I hypersensitivity)
 - ♦ treatment
 - moderate reaction: generalized urticaria, angioedema, wheezing, tachycardia
 - epinephrine (1:1000) 0.3-0.5 mg SC
 - antihistamines: diphenhydramine (Benadryl®) 25-50 mg IM
 - salbutamol (Ventolin®) 1 cc via nebulizer
 - severe reaction/evolution: severe wheezing, laryngeal/pulmonary edema, shock
 - ABCs, may need ETT due to airway edema
 - epinephrine (1:1000) 0.1-0.3 mg IV (or via ETT if no IV access) to start, repeat as needed
 - antihistamines: Benadryl® 50 mg IV (~1 mg/kg)
 - steroids: hydrocortisone (Solucortef®) 100 mg IV (~1.5 mg/kg) or methylprednisolone (Solumedrol®) 1 mg/kg IV q6h x 24h
 - large volumes of crystalloid may be required

g) drugs

- vasodilators, high spinal anesthetic interfering with sympathetic outflow

h) other

- transfusion reaction, Addisonian crisis, thyrotoxicosis, hypothyroid, aortocaval syndrome

Causes of Intraoperative Hypertension

- pain, anxiety due to inadequate anesthesia
- pre-existing essential hypertension, coarctation or pre-eclampsia
- hypoxemia/hypercarbia
- hypervolemia
- drugs (e.g. ephedrine, epinephrine, cocaine, phenylephrine, ketamine)
- allergic/anaphylactic reaction
- hypermetabolic states: malignant hyperthermia, neuroleptic malignant syndrome (see [Psychiatry](#), PS44), pheochromocytoma, thyroid storm (see [Endocrinology](#), E35, E25)

Fluid Balance and Resuscitation



- TOTAL REQUIREMENT = MAINTENANCE + DEFICIT + ONGOING LOSS
- in surgical settings this formula must take into account multiple factors including pre-operative fasting/decreased fluid intake, increased losses during or before surgery, fluid shifting during surgery, fluids given with blood products and medications

What is the Maintenance?

- average healthy adult requires approximately 2500 mL water/day
 - 200 mL/day GI losses
 - 800 mL/day insensible losses (respiration, perspiration)
 - 1500 mL/day urine (beware of renal failure)
- increased requirements with fever, sweating, GI losses (vomiting, diarrhea, NG suction), adrenal insufficiency, hyperventilation, and polyuric renal disease
- decreased requirements with anuria/oliguria, SIADH, highly humidified atmospheres, and CHF
- 4:2:1 rule to calculate maintenance requirements (applies to crystalloids only)
 - 4 mL/kg/hour first 10 kg
 - 2 mL/kg/hour second 10 kg
 - 1 mL/kg/hour for remaining weight >20 kg
- maintenance electrolytes
 - Na: 3 mEq/kg/day
 - K: 1 mEq/kg/day
- e.g. 50 kg patient maintenance requirements
 - fluid = $40 + 20 + 30 = 90$ mL/hour = 2160 mL/day
 - Na = 150 mEq/day (therefore 66 mEq/L)
 - K = 100 mEq/day (therefore 22 mEq/L)
- above patient's requirements roughly met with 2/3 D5W, 1/3 NS
 - e.g. 2/3 + 1/3 @ 100 mL/hour with 20 mEq KCl per litre

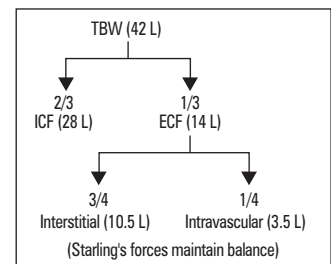


Figure 7. Total Body Water Division in a 70 kg Adult

What is the Deficit?

- patients should be adequately hydrated prior to anesthesia
- TBW = 60% or 50% of total body weight for an adult male or female, respectively (e.g. for a 70 kg adult male TBW = $70 \times 0.6 = 42$ L)
- total Na content determines ECF volume, [Na] determines ICF volume
- hypovolemia due to volume contraction
 - extra-renal Na loss
 - ♦ GI: vomiting, NG suction, drainage, fistulae, diarrhea
 - ♦ skin/resp: insensible losses (fever), sweating, burns
 - ♦ vascular: hemorrhage
 - renal Na and H₂O loss
 - ♦ diuretics
 - ♦ osmotic diuresis
 - ♦ hypoaldosteronism
 - ♦ salt-wasting nephropathies
 - renal H₂O loss
 - ♦ diabetes insipidus (central or nephrogenic)
 - hypovolemia with normal or expanded ECF volume
 - ♦ decreased cardiac output
 - ♦ redistribution
 - hypoalbuminemia: cirrhosis, nephrotic syndrome
 - capillary leakage: acute pancreatitis, rhabdomyolysis, ischemic bowel, sepsis, anaphylaxis
- replace water and electrolytes as determined by patient's needs
- with chronic hyponatremia correction must be done gradually over >48 hours to avoid CNS central pontine myelinolysis

Table 4. Signs and Symptoms of Dehydration

Percentage of Body Water Loss	Severity	Signs and Symptoms
3%	Mild	Decreased skin turgor, sunken eyes, dry mucous membranes, dry tongue, reduced sweating
6%	Moderate	Oliguria, orthostatic hypotension, tachycardia, low volume pulse, cool extremities, reduced filling of peripheral veins and CVP, hemoconcentration, apathy
9%	Severe	Profound oliguria or anuria and compromised CNS function with or without altered sensorium

What are the Ongoing Losses?

- tubes
 - Foley catheter, NG, surgical drains
- third spacing (other than ECF, ICF)
 - pleura, GI, retroperitoneal, peritoneal
 - evaporation via exposed viscera, burns
- blood loss
- ongoing loss due to surgical exposure and evaporative losses
 - minor surgery 3 cc/kg/hr e.g. laparoscopic surgery
 - intermediate surgery 6 cc/kg/hr e.g. open cholecystectomy
 - major surgery 9 cc/kg/hr e.g. abdominal aneurysm repair

IV Fluids

- replacement fluids include crystalloid and colloid solutions
- improves perfusion but NOT O₂ carrying capacity of blood

Crystalloid Infusion

- salt-containing solutions that distribute within ECF
- maintain euolemia in patient with blood loss: 3 mL crystalloid infusion per 1 mL of blood loss for volume replacement (i.e. 3:1 replacement). Controversy surrounds this as an initial vs. maximal replacement target
- after 3 L crystalloid replacement, switch to pRBCs
- if large volumes are to be given, use balanced fluids such as Ringer's lactate or Plasmalyte®, as too much normal saline (NS) may lead to hyperchloremic metabolic acidosis

Colloid Infusion (see *Blood Products*, A15)

- collected from donor blood (fresh frozen plasma, albumin, RBCs) or synthetics [e.g. hydroxyethyl starch (HES) solutions]
- distributes within intravascular volume
- 1:1 ratio (infusion: blood loss) only in terms of replacing volume
- HES colloids remain in intravascular space (metabolized by plasma serum amylase and renally excreted), two available in Canada: Voluven® and Pentaspan®

Table 5. Colloid HES Solutions

	Concentration	Plasma Volume Expansion	Duration (h)	Maximum Daily Dose (ml/kg)
Voluven®	6%	1:1	4-6	33-50
Pentaspan®	10%	1:1.2-1.5	18-24	28

Initial Distribution of IV Fluids

- H₂O follows ions/molecules to their respective compartments

Table 6. IV Fluid Solutions

		ECF	Ringer's Lactate	0.9 NS	0.45 NS	D5W	2/3 + 1/3	Plasmalyte
mEq/L	Na	142	130	154	77	-	51	140
	K	4	4	-	-	-	-	5
	Ca	4	3	-	-	-	-	-
	Mg	3	-	-	-	-	-	3
	Cl	103	109	154	77	-	51	98
	HCO ₃	27	28*	-	-	-	-	27
mOsm/L		280-310	273	308	407	253	269	294

*Converted from lactate

Colloids versus Crystalloids for Fluid Resuscitation in Critically Ill Patients
Cochrane Library 2009; Issue 3.**Purpose:** To evaluate the effects of colloids compared to crystalloids for fluid resuscitation, specifically when used in critically ill patients.**Methods:** A meta-analysis was performed looking at randomized controlled trials comparing colloid vs. crystalloids in use with patient requiring fluid resuscitation due to traumatic injury (including burns) or post surgery. Pregnant women and neonates were excluded. Primary outcome was overall mortality.**Results:** Results are broken down based on specific colloid. For albumin (or plasma protein fraction) the relative risk (RR) was 1.00 (95% CI 0.91 - 1.10), as compared to crystalloid. For hydroxyethyl starch the RR was 1.18 (95% CI 0.96 - 1.44). Modified gelatin had a RR of 0.91 (95% CI 0.49 - 1.72) and Dextran had a RR of 1.24 (95% CI 0.94 - 1.65). For colloids mixed in a hypertonic crystalloid as compared to isotonic crystalloid the RR was 0.88 (95% CI 0.74 - 1.05).**Conclusions:** There is no evidence that use of colloids improves survival in trauma patients, burn patients or post-operative patients, when compared to crystalloid solutions. Given the increased cost of colloids as compared to crystalloids, it is recommended that crystalloids be the fluid of choice in these patients.

Blood Products

- see Hematology, H50

Table 7. Blood Products

Red Blood Cells (RBCs) (U = unit)	<ul style="list-style-type: none"> • 1 U RBCs = approx. 300 mL • 1 U RBCs increases Hb by approx. 10 g/L in a 70 kg patient • RBCs may be diluted with colloid/crystalloid to decrease viscosity • Decision to transfuse based on initial blood volume, premorbid Hb level, present volume status, expected further blood loss, patient health status • MASSIVE transfusion = $> 1 \times \text{blood volume}/24 \text{ hours}$
Autologous RBCs	<ul style="list-style-type: none"> • Replacement of blood volume with one's own RBCs • May decrease complications (infectious, febrile, etc.) • Alternative to homologous transfusion in elective procedures, but only if adequate Hb and no infection • Pre-op phlebotomy prior to elective surgery (up to 4 U collected > 1 week before surgery) • Intraoperative salvage and filtration (cell saver); contraindicated in dirty cases
Non-RBC Products	<ul style="list-style-type: none"> • Fresh frozen plasma (FFP) <ul style="list-style-type: none"> ▪ Contains all plasma clotting factors and fibrinogen close to normal plasma levels ▪ To prevent/treat bleeding due to coagulation factor depletion/deficiencies, liver impairment • Cryoprecipitate <ul style="list-style-type: none"> ▪ Contains Factors VIII and XIII, vWF, fibrinogen • Platelets <ul style="list-style-type: none"> ▪ Used in thrombocytopenia, massive transfusions, impaired platelet function • Albumin <ul style="list-style-type: none"> ▪ Selective intravascular volume expander • Erythropoietin <ul style="list-style-type: none"> ▪ Can be used pre-operatively to stimulate erythropoiesis



Calculating Acceptable Blood Losses (ABL)

- Blood volume

term infant	80 mL/kg
adult male	70 mL/kg
adult female	60 mL/kg
- Calculate estimated blood volume (EBV) (e.g. in a 70 kg male, approx. 70 mL/kg)
 $EBV = 70 \text{ kg} \times 70 \text{ mL/kg} = 4900 \text{ mL}$
- Decide on a transfusion trigger, i.e. the Hb level at which you would begin transfusion, (e.g. 70 g/L for a person with $Hb(i) = 150 \text{ g/L}$)
 $Hb(f) = 70 \text{ g/L}$
- Calculate

$$ABL = \frac{Hb(i) - Hb(f)}{Hb(i)} \times EBV$$

$$= \frac{150 - 70}{150} \times 4900 = 2613 \text{ mL}$$
- Therefore in order to keep the Hb level above 70 g/L, RBCs would have to be given after approximately 2.6 L of blood has been lost.

Transfusion Reactions

Immunosuppression

- some studies show associations between peri-operative transfusion and post-operative infection, earlier cancer recurrence, and poorer outcome

Nonimmune

- infectious risks: HIV, hepatitis B/C, Epstein-Barr virus (EBV), cytomegalovirus (CMV), brucellosis, malaria, salmonellosis, measles, syphilis
- hypervolemia
- electrolyte changes: increased K in stored blood
- dilutional coagulopathy
- dilutional thrombocytopenia
- hypothermia
- citrate toxicity
- hypocalcemia
- iron overload

A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care
NEJM 1999; 340: 409-417

Purpose: To determine whether a restrictive strategy of RBC transfusion and a liberal strategy produce equivalent results in critically ill patients.
Study: Randomized controlled trial with 60 day follow-up.

Patients: 838 critically ill patients with euvoemia after initial treatment who had Hb concentrations of less than 90 g/L within 72 hours after admission to the ICU. Mean age 57.5 years, 62.5% male.

Intervention: Patients were randomly assigned to either a restrictive strategy of transfusion, in which RBC were transfused if the Hb dropped <70 g/L and Hb concentrations were maintained between 70-90 g/L, or to a liberal strategy, in which transfusions were given when the Hb dropped <100 g/L and Hb concentrations were maintained between 100-120 g/L.

Main Outcomes: All cause mortality rates at 30 and 60 days, mortality rates during the stay in ICU and hospitalization, survival times during the first 30 days, and rates of organ failure and dysfunction.

Results: Overall, 30-day mortality was similar in the two groups. However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill (8.7% vs. 16.1%) and who were less than 55 years of age (5.7% vs. 13%), but not among patients with clinically significant cardiac disease.

The mortality rate during hospitalization was significantly lower in the restrictive-strategy group (22.2% vs. 28.1%).

Conclusions: A restrictive strategy of RBC transfusion is at least as effective as, and possibly superior to, a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute MI and unstable angina.

Table 8. Immune Transfusion Reactions

Reaction	Cause	Presentation	Management
Non-hemolytic: Febrile	<ul style="list-style-type: none"> Alloantibodies to WBC, platelet, or other donor plasma antigens 	<ul style="list-style-type: none"> Mild fever <38°C with or without rigors; may be >38°C with restlessness and shivering Nausea, facial flushing, headache, myalgias, hypotension, chest and back pain Occurs quickly; near completion of transfusion or within 2 hours 1 in 100 	<ul style="list-style-type: none"> Rule out fever due to hemolytic reaction or bacterial contamination Mild (<38°C): decrease infusion rate and give antipyretics Severe: stop transfusion, give antipyretics, antihistamines, and symptomatic treatment
Non-hemolytic: Allergic	<ul style="list-style-type: none"> Mild allergic reaction due to IgE alloantibodies to substances in donor plasma Mast cells activated with histamine release Usually occurs in pre-exposed (e.g. multiple transfusions, multiparous) 	<ul style="list-style-type: none"> Often have history of similar reactions Abrupt onset pruritic erythema/urticaria on arms and trunk, occasionally with fever Less common: involvement of face, larynx and bronchioles 1 in 100 	<ul style="list-style-type: none"> Mild: slow transfusion rate, IV antihistamines Moderate to severe: stop transfusion, IV antihistamines, subcutaneous epinephrine, hydrocortisone, IV fluids, bronchodilators Prophylactic: antihistamines 15-60 minutes prior to transfusion, washed or deglycerolized frozen RBC
Non-hemolytic: Anaphylactoid	<ul style="list-style-type: none"> In IgA deficient patients with anti-IgA antibodies receiving IgA-containing blood Immune complexes activate mast cells, basophils, eosinophils, and complement system = severe symptoms after transfusion of RBC, plasma, platelets, or other components with IgA 	<ul style="list-style-type: none"> Rare, potentially lethal Apprehension, urticarial eruptions, dyspnea, hypotension, laryngeal and airway edema, wheezing, chest pain, shock, sudden death 	<ul style="list-style-type: none"> Circulatory support with fluids, catecholamines (epinephrine), bronchodilators Respiratory assistance as indicated Evaluate for IgA deficiency and anti-IgA antibodies Future transfusions must be free of IgA: washed/deglycerolized RBCs free of IgA, blood from IgA deficient donor
Transfusion Related Acute Lung Injury (TRALI)	<ul style="list-style-type: none"> Form of noncardiogenic pulmonary edema Immunologic cause; not due to fluid overload or cardiac failure Binding of donor Ab against recipient WBC causing cytokine release leading to increased capillary permeability 	<ul style="list-style-type: none"> Occurs 2-4 hours post transfusion Respiratory distress: mild dyspnea to severe hypoxia Chest x-ray: consistent with acute pulmonary edema, but pulmonary artery and wedge pressures are not elevated 1 in 5000 	<ul style="list-style-type: none"> Usually resolves within 48 hrs with O₂, mechanical ventilation, supportive treatment
Hemolytic Acute (intravascular hemolysis)	<ul style="list-style-type: none"> Caused by donor incompatibility with recipient's blood Often due to clerical error Antibody coated RBC is destroyed by activation of complement system ABO incompatibility common cause, other RBC Ag-Ab systems can be involved 	<ul style="list-style-type: none"> Fever, chills, chest or back pain, hypotension, tachycardia, nausea, flushing, dyspnea, wheezing, hypoxemia, hemoglobinuria, diffuse bleeding due to DIC, acute renal failure <1 in 250 000 	<ul style="list-style-type: none"> Stop transfusion Notify blood bank, confirm or rule out diagnosis – clerical check, direct Coombs', repeat grouping, Rh screen and crossmatch, serum haptoglobin Manage hypotension with fluids, inotropes, other blood products Maintain urine output with crystalloids, furosemide, dopamine, alkalinize urine Component treatment if DIC, repeat grouping, Rh screen and crossmatch, serum haptoglobin Manage hypotension with fluids, inotropes, other blood products Component treatment (e.g. FFP, cryoprecipitate)
Hemolytic Delayed (extravascular hemolysis)	<ul style="list-style-type: none"> Caused by donor incompatibility with recipient's blood Generally mild, caused by antibodies to Rh system, Kell, Duffy, or Kidd antigens The level of antibody at the time of transfusion is too low to be detected or to cause hemolysis, later the level of antibody is increased due to secondary stimulus 	<ul style="list-style-type: none"> Occurs in recipients sensitized to RBC antigens by previous blood transfusion or pregnancy Anemia, mild jaundice, fever 1 to 21 days post transfusion 	<ul style="list-style-type: none"> Supportive Direct Coombs, a reexamination of pretransfusion specimens from the patient and donor for diagnosis

Extubation

- performed by trained, experienced personnel because reintubation may be required
- criteria
 - patient must no longer have intubation requirements
 - patency: airway must be patent
 - protection: patient must have intact airway reflexes
 - patient must be oxygenating and ventilating spontaneously
- laryngospasm more likely in semiconscious patient; must ensure adequate LOC
- general guidelines
 - ensure patient has normal neuromuscular function and hemodynamic status
 - ensure patient is breathing spontaneously with adequate rate and tidal volume
 - allow ventilation (spontaneous or controlled) with 100% O₂ for 3-5 minutes
 - suction secretions from pharynx
 - deflate cuff, remove ETT on inspiration (vocal cords abducted)
 - ensure patient is breathing adequately after extubation
 - ensure face mask for O₂ delivery available
 - proper positioning of patient during transfer to recovery room (e.g. lateral decubitus, head elevated)

Complications of Extubation

- early
 - aspiration
 - laryngospasm
- late
 - transient vocal cord incompetence
 - edema (glottic, subglottic)
 - pharyngitis, tracheitis

Post-Operative Care

- pain management should be continuous from OR to post-anesthetic unit (PAU) to hospital ward and home
- pain service may assist with management of post-operative inpatients

Post-Operative Nausea and Vomiting (PONV)

- hypotension and bradycardia must be ruled out
- pain and surgical manipulation also cause nausea
- often treated with dimenhydrinate (Gravol®), metoclopramide (Maxeran®) (not with bowel obstruction), prochlorperazine (Stemetil®), ondansetron (Zofran®), granisetron (Kytril®)

Post-Operative Confusion and Agitation

- ABCs first! – confusion or agitation can be caused by airway obstruction, hypercapnea, hypoxemia
- neurologic status (Glasgow Coma Scale, pupils), residual paralysis from anesthetic
- pain, distended bowel/bladder
- fear/anxiety/separation from caregivers/language barriers
- metabolic disturbance (hypoglycemia, hypercalcemia, hyponatremia – especially post-TURP)
- intracranial cause (stroke, raised intracranial pressure)
- drug effect (ketamine, anticholinergics)
- elderly patients are more susceptible to post-operative delirium

Pain Management

Definitions

- nociception: detection, transduction and transmission of noxious stimuli
- pain: perception of nociception which occurs in the brain

Acute Pain

- pain of short duration (<6 weeks) usually associated with surgery, trauma or acute illness; often associated with inflammation
- usually limited to the area of damage/trauma and resolves with healing



Risk Factors for Post-Operative Nausea and Vomiting (PONV)

- Young age
- Female
- History of PONV
- Non-smoker
- Type of surgery: ophtho, ENT, abdo/pelvic, plastics
- Type of anesthetic: N₂O, opioids, volatile agents

Drugs for Preventing Post-Operative Nausea and Vomiting.

Cochrane Library 2008; Issue 4.

Purpose: To evaluate the efficacy of antiemetics in preventing nausea and vomiting in post-operative patients.

Methods: A meta-analysis was performed looking at randomized controlled trials comparing an antiemetic to either a second antiemetic or placebo. Trials looking at dosing and/or timing of medication administration were also included. Post-operative nausea or vomiting was used as the primary outcome.

Results: 737 studies involving 103 237 patients. Eight drugs significantly reduced the occurrence of post-operative nausea and vomiting, namely: droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron. Relative risk (RR) versus placebo varied between 0.60 and 0.80. Side effects included a significant increase in drowsiness for droperidol (RR 1.32) and headache for ondansetron (1.16). The cumulative number needed to treat was 3.57.

Conclusion: Antiemetic medication is effective for reducing the occurrence of post-operative nausea and vomiting. However, further investigation needs to be done to determine whether antiemetics can cause more severe (and likely rare) side-effects, which could alter how liberally they are used.

**WHO Analgesia Ladder****Mild Pain**

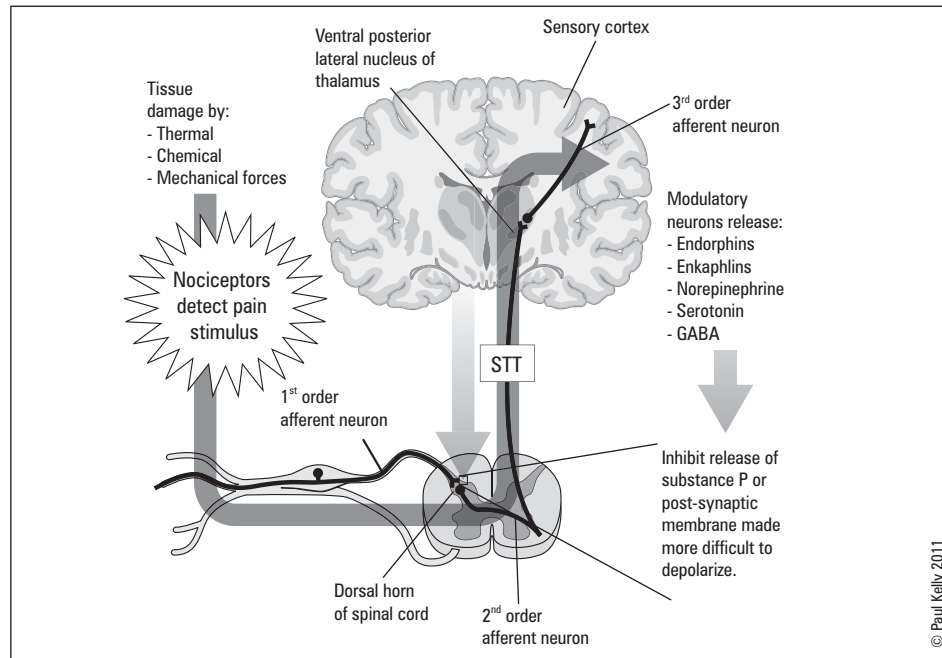
Acetaminophen
NSAIDS

Moderate Pain

Codeine
Oxycodone

Severe Pain

Oxycodone
Morphine
Hydromorphone
Fentanyl

**Figure 8. Acute Pain Mechanism****Pharmacological Management of Acute Pain**

- ask the patient to rate the pain out of 10, or using visual analog scale, to determine severity

Table 9. Commonly Used Analgesics

	Acetaminophen	NSAIDs	Opioids
Examples	• Tylenol®	• Aspirin®, ibuprofen, naproxen • ketorolac (IV)	• Oral: codeine, oxycodone, morphine, hydromorphone • Parenteral: morphine, hydromorphone, fentanyl
Indications	• First-line for mild acute pain	• Mild-moderate pain	• Oral: mild and moderate acute pain • Parenteral: severe acute pain
Mechanism of Action	• ? Cyclooxygenase-2 (COX-2) inhibition • ? Modulation of endogenous cannabinoid system	• Non-selective COX-1 and -2 inhibition reducing proinflammatory prostaglandin synthesis	• Dampens nociceptive transmission between 1 st and 2 nd order neurons in the dorsal horn • Activates ascending modulatory pathways resulting in release of inhibitory neurotransmitters • Inhibits peripheral inflammatory response and hyperalgesia • Affects mood and anxiety – alleviates the affective component of perceived pain
Dosing/Administration	• Limited by analgesic ceiling beyond which there is no additional analgesia • Opioid-sparing • Max dose of 4 g/24hrs	• Limited by analgesic ceiling beyond which there is no additional analgesia • Opioid-sparing • Significant inter-individual variation in efficacy	• No analgesic ceiling (except for codeine) • Can be administered intrathecal (spinal block) or by continuous infusion • See <i>Clinical Pharmacology</i> , CP14 for opioid analgesic equivalencies
Side Effects/Toxicity	• Considered relatively safe • Liver toxicity in elevated doses	• Gastric ulceration/bleeding • Decreased renal perfusion • Photosensitivity • Premature closure of the ductus arteriosus in pregnancy	• Respiratory depression • Constipation and abdominal pain • Sedation • Nausea and vomiting • Pruritus • Confusion (particularly in the elderly)

**Use NSAIDs with Caution in Patients with:**

1. Asthma
2. Coagulopathy
3. GI ulcers
4. Renal insufficiency
5. Pregnancy, 3rd trimester

**Common Side Effects of Opioids**

1. Nausea and vomiting
2. Constipation
3. Sedation
4. Pruritis
5. Abdominal pain
6. Urinary retention
7. Respiratory depression

**PCA Parameters**

1. Loading dose
2. Bolus dose
3. Lockout interval
4. Continuous infusion (optional)
5. Max. 4 hr limit (optional)

**Advantages of PCA**

- Better pain control
- Fewer side effects
- Accommodates patient variability
- Accommodates changes in opioid requirements

- patient controlled analgesia (PCA)
 - involves the use of computerized pumps that can deliver a constant infusion as well as bolus breakthrough doses of parenterally-administered opioid analgesics
 - limited by lockout intervals
 - most commonly used agents: morphine and hydromorphone
 - refer to Table 12 for suggested infusion rate, PCA dose, and lockout intervals

Opioid Antagonists (naloxone, naltrexone)

- opioid overdose manifests primarily at CNS (e.g. respiratory depression) – manage ABCs
- opioid antagonists competitively inhibit opioid receptors, predominantly Mu (μ) receptors
- naloxone is short acting ($t_{1/2} = 1$ hr); effects of narcotic may return when naloxone wears off, therefore the patient must be observed closely following its administration
- naltrexone is longer acting ($t_{1/2} = 10$ hrs); less likely to see return of narcotic effects
- relative overdose of naloxone may cause nausea, agitation, sweating, tachycardia, hypertension, re-emergence of pain, pulmonary edema, seizures (essentially opioid withdrawal)

Regional Anesthesia



Definition of Regional Anesthesia

- local anesthetic agent (LA) applied around a peripheral nerve at any point along the length of the nerve (from spinal cord up to, but not including, the nerve endings) for the purposes of reducing or preventing impulse transmission
- no CNS depression (unless overdose of local anesthetic); patient conscious
- regional anesthetic techniques categorized as follows:
 - epidural and spinal anesthesia (neuraxial anesthesia)
 - peripheral nerve blockades
 - IV regional anesthesia (e.g. Bier block)

Preparation for Regional Anesthesia

Patient Preparation

- thorough pre-operative evaluation and assessment of patient
- technique explained to patient
- IV sedation may be indicated before block
- monitoring should be as extensive as for general anesthesia

Relative Indications for Regional Anesthesia

- avoids some of the dangers of general anesthesia, e.g. known difficult intubation, severe respiratory failure, etc.
- patient specifically requests regional anesthesia
- high quality post-operative pain relief
- general anesthesia not available/contraindicated
- titration of LA dosage for differential blockade, e.g. can block pain but preserve motor function

Complications of Regional Anesthesia

- failure of technique/inadequate anesthesia
- systemic drug toxicity due to overdose or intravascular injection
- injury to muscle, ligament or bone (back pain), to nerve root/spinal cord (nerve deficit), to epidural vein (hematoma)
- infection (e.g. osteitis, epidural abscess, meningitis)
- spinal and epidural: sympathetic blockade causing hypotension and bradycardia (occurs early, followed by sensory then motor blockade)

Epidural and Spinal Anesthesia

Anatomy of Spinal/Epidural Area (Figure 9)

- spinal cord extends to L2, dural sac to S2 in adults
- nerve roots (cauda equina) from L2 to S2
- needle inserted below L2 should not encounter cord, thus L3-L4, L4-L5 interspace commonly used
- structures penetrated
 - skin
 - subcutaneous fat
 - supraspinous ligament
 - interspinous ligament
 - ligamentum flavum (last layer before epidural space)
 - dura + arachnoid for spinal anesthesia

Patient Controlled Opioid Analgesia versus Conventional Opioid Analgesia for Postoperative Pain.

Cochrane Library 2009; Issue 1.

Purpose: To evaluate the efficacy of patient controlled analgesia (PCA) as compared to conventional 'as-needed' analgesia administration providing pain relief in post-operative patients.

Methods: Meta-analyses of randomised controlled trials comparing PCA versus conventional administration of opioid analgesia. Assessment employed a visual analog scale (VAS) for pain intensity along with overall analgesic consumption, patient satisfaction, length of stay and adverse side-effects.

Results: 55 studies with a total of 2023 patients receiving PCA and 1838 patients with standard as-needed opioid administration. PCA provided significantly better pain control through 72 hours post-operatively, but patients consumed significantly more opioids (+7 mg morphine / 24 hr, $P < 0.05$). Significantly more patients reported pruritis in the PCA group compared to control with a number needed to harm of 13. No significant difference in overall length of stay in hospital, sedation level, nausea/vomiting or urinary retention.

Conclusions: Patient controlled opioid analgesia is more effective than standard as-needed administration for reducing post-operative pain. However, patients using PCA consume more opioids overall and have more pruritis.

**Benefits of Regional Anesthesia**

- Reduced peri-op pulmonary complications
- Reduced peri-op analgesia requirements
- Decreased PONV
- Reduced peri-op blood loss
- Ability to monitor CNS status during procedure
- Improved perfusion
- Lower incidence of VTE

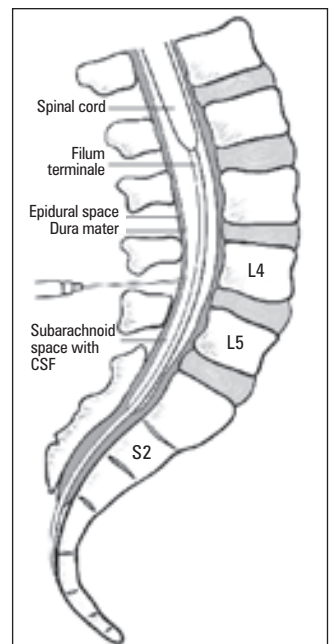


Figure 9. Landmarks for Placement of Epidural/Spinal



Landmarking Epidural/Spinal Anesthesia

Spinous processes should be maximally flexed

L4 spinous processes found between iliac crests

Common sites of insertion are L3-L4 and L4-L5



Classic Presentation of Dural Puncture Headache

1. Onset 6 hrs – 3 days after dural puncture
2. Postural component (worse sitting)
3. Occipital or frontal localization
4. \pm tinnitus, diplopia

Reduction of Postoperative Mortality and Morbidity with Epidural or Spinal Anaesthesia: Results from Overview of Randomised Trials

BMJ 2000; 321:1-12
Purpose: To obtain reliable estimates of the effects of neuraxial blockade with epidural or spinal anesthesia on postoperative morbidity and mortality.

Study: Systematic review of all trials with randomization to intra-operative neuraxial blockade versus not.

Patients: 141 trials including 9559 patients.

Main Outcomes: All cause mortality, MI, PE, DVT, transfusion requirements, pneumonia, other infections, respiratory depression, and renal failure.

Results: Overall mortality was reduced by about a third in patients allocated to neuraxial blockade. Neuraxial blockade reduced the risk of PE by 55%, DVT by 44%, transfusion requirements by 50%, pneumonia by 39%, and respiratory depression by 59%. There were also reductions in MI and renal failure. The proportional reductions in mortality did not clearly differ by surgical group, type of blockade (epidural or spinal), or in those trials in which neuraxial blockade was combined with general anesthesia compared with trials in which neuraxial blockade was used alone.

Conclusions: Neuraxial blockade reduces postoperative mortality and other serious complications.

Table 10. Epidural versus Spinal Anesthesia

	Epidural	Spinal
Deposition Site	LA deposited in epidural space (space between ligamentum flavum and dura) Initial blockade is at the spinal roots followed by some degree of spinal cord anesthesia as LA diffuses into the subarachnoid space through the dura	LA injected into subarachnoid space in the dural sac surrounding the spinal cord and nerve roots
Onset	Significant blockade requires 10-15 minutes Slower onset of side effects	Rapid blockade (onset in 2-5 minutes)
Effectiveness	Effectiveness of blockade can be variable	Very effective blockade
Difficulty	Technically more difficult; greater failure rate	Easier to perform due to visual confirmation of CSF flow
Patient Positioning	Position of patient not as important; specific gravity not an issue	Hyperbaric LA solution – position of patient important
Specific Gravity/Spread	Solutions injected here spread throughout the potential space; specific gravity of solution does not affect spread	LA solution may be made hyperbaric (of greater specific gravity than the cerebrospinal fluid by mixing with 10% dextrose, thus increasing spread of LA to the dependent (low) areas of the subarachnoid space)
Dosage	Larger volume/dose of LA (usually > toxic IV dose)	Smaller dose of LA required (usually < toxic IV dose)
Continuous Infusion	Use of catheter allows for continuous infusion or repeat injections	None
Complications	Failure of technique Hypotension Bradycardia if cardiac sympathetics blocked (only if ~T2-4 block) Epidural or subarachnoid hematoma Accidental subarachnoid injection can produce spinal anesthesia (and any of the above complications) Systemic toxicity of LA (accidental intravenous) Catheter complications (shearing, kinking, vascular or subarachnoid placement) Infection Dural puncture	Failure of technique Hypotension Bradycardia if cardiac sympathetics blocked (only if ~T2-4 block), i.e. "high spinal" Epidural or subarachnoid hematoma Post-spinal headache (CSF leak) Persistent paresthesias (usually transient) Spinal cord trauma, infection
Combined Spinal-Epidural	Combines the benefits of rapid, reliable, intense blockade of spinal anesthesia together with the flexibility of an epidural catheter	

LA = Local anesthetic agent

Contraindications to Spinal/Epidural Anesthesia

- absolute contraindications
 - lack of proper equipment or properly trained personnel
 - lack of IV access
 - allergy to LA
 - infection at puncture site or underlying tissues
 - coagulopathies
 - raised ICP
 - sepsis/bacteremia
 - hemodynamic instability/uncorrected hypovolemia
- relative contraindications
 - bacteremia
 - pre-existing neurological disease
 - aortic/mitral valve stenosis (i.e. fixed cardiac output states)
 - previous spinal surgery, severe kyphoscoliosis
 - severe/unstable psychiatric disease or emotional instability

Peripheral Nerve Blocks

- generally used for post-operative analgesia; sometimes uses for intra-operative anesthesia
- relatively safe
- 2 cardinal rules: 1. Avoid intraneural injection 2. Avoid neurotoxic agents
- e.g. brachial plexus block, femoral nerve block, digital ring block, etc.
- can be ultrasound-guided to prevent neural injury

Contraindications to Peripheral Nerve Blockade

- allergy to local anesthetic (LA)
- patient refusal, lack of cooperation
- lack of resuscitation equipment
- lack of IV access
- certain types of pre-existing neurological dysfunction (e.g. ALS, MS)
- local infection at block site

Local Anesthesia

Local Anesthetic Agents (LA)

- see Table 17 for list of local anesthetic agents

Definition and Mode of Action

- LA are drugs that block the generation and propagation of impulses in excitable tissues: nerves, skeletal muscle, cardiac muscle, brain
- LA bind to receptor (on the cytosolic side of the Na channel, i.e. lipid soluble), inhibiting Na flux and thus blocking impulse conduction
- different types of nerve fibres undergo blockade at different rates

Absorption, Distribution, Metabolism

- LA readily crosses the blood-brain barrier (BBB) once absorbed into the bloodstream
- **ester-type** LA (procaine, tetracaine) are broken down by plasma and hepatic esterases; metabolites excreted via kidneys
- **amide-type** LA (lidocaine, bupivacaine) are broken down by hepatic mixed-function oxidases (P450 system); metabolites excreted via kidneys

Selection of LA

- choice of LA depends on
 - onset of action: influenced by pKa (the lower the pKa, the higher the concentration of the base form of the LA and the faster the onset of action)
 - duration of desired effects: influenced by protein binding (longer duration of action when protein binding of LA is strong)
 - potency: influenced by lipid solubility (agents with high lipid solubility penetrate the nerve membrane more easily)
 - unique needs (e.g. sensory blockade with relative preservation of motor function by bupivacaine at low doses)
 - potential for toxicity

Systemic Toxicity

- see Table 17 for max doses, potency and duration of action for common LA agents
- occurs by accidental intravascular injection, LA overdose, or unexpectedly rapid absorption
- CNS effects first appear to be excitatory due to initial block of inhibitory fibres; then subsequent block of excitatory fibres
- CNS effects (in order of appearance) (Figure 10)
 - numbness of tongue, perioral tingling, metallic taste
 - disorientation, drowsiness
 - tinnitus
 - visual disturbances
 - muscle twitching, tremors
 - unconsciousness
 - convulsions, seizures
 - generalized CNS depression, coma, respiratory arrest
- CVS effects
 - vasodilation, hypotension
 - decreased myocardial contractility

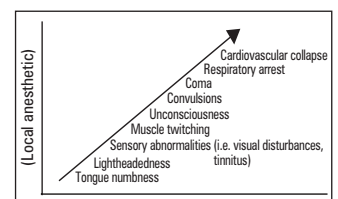


Figure 10. Local Anesthetic Systemic Toxicity

- dose-dependent delay in cardiac impulse transmission
 - ♦ prolonged PR, QRS intervals
 - ♦ sinus bradycardia
- CVS collapse
- treatment of systemic toxicity
 - early recognition of signs
 - 100% O₂, manage ABCs
 - diazepam or sodium thiopental may be used to increase seizure threshold
 - if the seizures are not controlled by diazepam or thiopental, consider using succinylcholine (stops muscular manifestations of seizures, facilitates intubation)
 - manage arrhythmias
 - consider Intralipid® 20% to bind local anesthesia in circulation

Local Infiltration, Hematoma Blocks

Local Infiltration

- injection of tissue with local anesthetic agent (LA), producing a lack of sensation in the infiltrated area due to LA acting on nerve endings
- suitable for small incisions, suturing, excising small lesions
- can use fairly large volumes of dilute LA to infiltrate a large area
- low concentrations of epinephrine (1:100,000-1:200,000) cause vasoconstriction, thus reducing bleeding and prolonging the effects of LA by reducing systemic absorption

Fracture Hematoma Block

- special type of local infiltration for pain control during manipulation of certain fractures
- hematoma created by fracture is infiltrated with LA to anesthetize surrounding tissues
- sensory blockade may be only partial
- no muscle relaxation

Topical Anesthetics

- various preparations of local anesthetics available for topical use, may be a mixture of agents, e.g. EMLA cream is a combination of 2.5% lidocaine and prilocaine
- must be able to penetrate the skin or mucous membrane

Obstetrical Anesthesia

Physiologic Changes in Pregnancy

1. **airway**
 - upper airway becomes edematous and friable
 - decreased FRC and increased O₂ consumption → desaturation
2. **cardiovascular system**
 - increased blood volume > increased RBC mass → mild anemia
 - decreased SVR proportionately greater than increased CO → decreased BP
 - prone to decreased BP due to aortocaval compression
3. **central nervous system**
 - decreased MAC due to hormonal effects
 - increased block height due to engorged epidural veins
4. **gastrointestinal system**
 - delayed gastric emptying
 - increased volume and acidity of gastric fluid
 - decreased LES tone
 - increased abdominal pressure
 - combined, these lead to an increased risk of aspiration

Options for Analgesia during Labour

1. **psychoprophylaxis** – Lamaze method
 - patterns of breathing and focused attention on fixed object
2. **systemic medication**
 - easy to administer, but risk of maternal or neonatal depression
 - common drugs: opioids (morphine, meperidine)
3. **inhalational analgesia**
 - easy to administer, makes uterine contractions more tolerable, but does not relieve pain completely
 - 50% nitrous oxide



Where Not to Use Local Anesthetic Agent (LA) with Epinephrine
 "Fingers, Toes, Penis, Nose"

The Effect of Epidural Analgesia on Labour, Maternal, and Neonatal Outcomes: A Systematic Review

Am J Obstet Gynecol 2002; 186:S69-77

Study: Meta-analysis of 14 studies with 4324 women.

Selection Criteria: Randomized controlled trials and prospective cohort studies between 1980-2001 comparing epidural analgesia to parenteral opioid administration during labour.

Types of Participants: Healthy women with uneventful pregnancies.

Intervention: Participants were randomized to either epidural analgesia or parenteral opioid administration during labour.

Outcomes and Results: Maternal – there were no differences between the 2 groups in first-stage labour length, incidence of Caesarean delivery, incidence of instrumented vaginal delivery for dystocia, nausea, or mid-to-low back pain post-partum. However, second-stage labour length was longer (mean = 15 min) and there were greater reports of fever and hypotension in the epidural group. Also, lower pain scores and greater satisfaction with analgesia were reported among the epidural group. There was no difference in lactation success at 6 weeks and urinary incontinence was more frequent in the epidural group immediately post-partum, but not at 3 months or 1 year (evidence from PC studies only). Neonatal – there were no differences between the 2 groups for incidence of fetal heart rate abnormalities, intrapartum meconium, poor 5-min Apgar score, or low umbilical artery pH. However, the incidence of poor 1-min Apgar scores and need for neonatal naloxone were higher in the parenteral opioid group.

Conclusions: Epidural analgesia is a safe intrapartum method for labour pain relief and women should not avoid epidural analgesia for fear of neonatal harm, Caesarean delivery, breastfeeding difficulties, long-term back pain or long-term urinary incontinence.

4. regional anesthesia

- provides excellent analgesia with minimal depressant effects
- hypotension is the most common complication
- maternal BP monitored q2-5 min for 15-20 min after initiation and regularly thereafter
- epidural usually given as it preferentially blocks sensation, leaving motor function intact

Options for Caesarean Section

- regional:** spinal or epidural
- general:** used if contraindications or time precludes regional blockade

Potential complications of anesthesia in Caesarean section:

- aspiration under general anesthesia: due to increased gastroesophageal reflux
- hypotension and/or fetal distress: caused by aortocaval compression; corrected by turning patient into the left lateral decubitus (LLD) position or using left uterine displacement (LUD)
- unintentional total spinal anesthesia
- LA-induced seizures: due to intravascular injection of LA
- post-dural puncture headache
- nerve injury (rare)



Nociceptive Pathways in Labour and Delivery

Labour

- Cervical dilation and effacement
- Visceral nerve fibres entering the spinal cord at T10-L1

Delivery

- Distention of lower vagina and perineum
- Somatic nociceptive impulses via the pudendal nerve entering the spinal cord at S2-S4

Pediatric Anesthesia

Respiratory System

- in comparison to adults, anatomical differences in infants include (Figure 11)
 - large head, short trachea/neck, large tongue, adenoids and tonsils
 - narrow nasal passages (obligate nasal breathers until 5 months)
 - narrowest part of airway at the level of the cricoid vs. glottis in adults
 - epiglottis is longer, U shaped and angled at 45 degrees; carina is wider and is at the level of T2 (T4 in adults)
- physiologic differences include
 - faster RR, immature respiratory centres which are depressed by hypoxia/hypercapnea (airway closure occurs in the neonate at the end of expiration)
 - less oxygen reserve during apnea – decreased total lung volume, vital and functional reserve capacity together with higher metabolic needs
 - greater V/Q mismatch – lower lung compliance due to immature alveoli (mature at 8 years)
 - greater work of breathing – greater chest wall compliance, weaker intercostals/diaphragm and higher resistance to airflow
- a pediatric breathing unit is required for all children <20 kg

Cardiovascular System

- blood volume at birth is approximately 80 mL/kg; transfusion should be started if >10% of blood volume lost
- children have a high pulse rate and low BP
- CO is increased by increasing HR, not stroke volume because of low heart wall compliance; therefore, bradycardia → severe compromise in CO

Temperature Regulation

- vulnerable to hypothermia
- minimize heat loss by use of warming blankets, covering the infant's head, humidification of inspired gases and warming of infused solutions

Central Nervous System

- the MAC of halothane is increased compared to the adult (i.e. 0.75% adult, 0.87% neonates, 1.2% infant)
- the neuromuscular junction is immature for the first 4 weeks of life and thus there is an increased sensitivity to non-depolarizing relaxants
- parasympathetics mature at birth, sympathetics mature at 4-6 months → autonomic imbalance
- infant brain is 12% of body weight and receives 34% of CO (adult: 2% body weight and 14% CO)

Glucose Maintenance

- infants less than 1 year can become seriously hypoglycemic during pre-operative fasting and post-operatively if feeding is not recommenced as soon as possible
- after 1 year children are able to maintain normal glucose homeostasis in excess of 8 hours



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- Larger tongue in proportion to mouth
- Smaller pharynx
- Larger and more flaccid epiglottis
- Larynx is more superior and anterior
- Narrowest point at cricoid cartilage
- Trachea is more narrow and less rigid

Figure 11. Comparison of Pediatric vs. Adult Airway



To increase alveolar minute ventilation in neonates, increase respiratory rate, not tidal volume.

Neonate 30-40 bpm

1-13 yrs $(24 - \frac{\text{age}}{2})$
min



ETT Sizing in Pediatrics

Diameter of tracheal tube in children (mm) after 1 year = $\frac{\text{age}}{4} + 4$

Length of tracheal tube (cm) = $\frac{\text{age}}{2} + 12$

Pharmacology

- higher dose requirements because of higher TBW (75% vs. 60% in adults) and greater volume of distribution
- barbiturates/opioids more potent due to greater permeability of BBB
- muscle relaxants
 - non-depolarizing
 - ♦ immature NMJ, variable response
 - depolarizing
 - ♦ must pretreat with atropine or may experience profound bradycardia, sinus node arrest due to PNS > SNS (also dries oral secretions)
 - ♦ more susceptible to arrhythmias, hyperkalemia, rhabdomyolysis, myoglobinemia, masseter spasm, and malignant hyperthermia

Uncommon Complications

Malignant Hyperthermia (MH)

- hypermetabolic disorder of skeletal muscle
- due to an uncontrolled increase in intracellular Ca (because of an anomaly of the ryanodine receptor which regulates the Ca channel in the sarcoplasmic reticulum of skeletal muscle)
- autosomal dominant (AD) inheritance
- incidence of 1-5:100,000, may be associated with skeletal muscle abnormalities such as dystrophy or myopathy
- anesthetic drugs triggering MH crises
 - volatile anesthetics: any drug ending in “-ane”
 - depolarizing relaxants: succinylcholine (SCh), decamethonium

Clinical Picture

- onset: immediate or hours after contact with trigger agent
 - increased oxygen consumption
 - increased end-tidal CO₂ on capnograph
 - tachycardia/dysrhythmia
 - tachypnea/cyanosis
 - increased temperature (late sign)
 - hypertension
 - diaphoresis
- muscular symptoms
 - trismus (masseter spasm) common but not specific for MH (occurs in 1% of children given SCh with halothane anesthesia)
 - tender, swollen muscles due to rhabdomyolysis
 - trunk or total body rigidity

Complications

- death
- coma
- disseminated intravascular coagulation (DIC)
- muscle necrosis/weakness
- myoglobinuric renal failure/hepatic dysfunction
- electrolyte abnormalities (e.g. hyperkalemia) and secondary arrhythmias
- ARDS
- pulmonary edema

Prevention

- suspect MH in patients with a family history of problems/death with anesthetic
- dantrolene prophylaxis no longer routine
- avoid all trigger medications (use regional if possible) and use “clean” equipment
- central body temp and end-tidal CO₂ monitoring

Malignant Hyperthermia Management [Based on Malignant Hyperthermia Association of the U.S. (MHAUS) Guidelines, 2008]

1. notify surgeon, discontinue volatile agents and succinylcholine, hyperventilate with 100% oxygen at flows of 10 L/min or more; halt the procedure as soon as possible
2. dantrolene 2.5 mg/kg rapidly IV, through large-bore IV if possible
 - repeat until there is control of signs of MH; sometimes up to 30 mg/kg is necessary
3. bicarbonate 1-2 mEq/kg if blood gas values are not available for metabolic acidosis

**Signs of Malignant Hyperthermia**

- Unexplained rise in end-tidal CO₂
- Increase in minute ventilation
- Tachycardia
- Hyperthermia (late sign)
- Rigidity

**Basic Principles of MH Management**

- CALL FOR HELP
- Turn off potential triggering agents
- Notify operating personnel
- Administer dantrolene 2.5 mg/kg q5minutes
- Cool patient to 38°C
- Monitor and correct blood gases, electrolytes, and glucose

4. cool the patients with core temp $>39^{\circ}\text{C}$
 - lavage open body cavities, stomach, bladder, rectum, apply ice to surface, infuse cold saline IV
 - stop cooling if temp is $<38^{\circ}\text{C}$ and falling to prevent drift to $<36^{\circ}\text{C}$
5. dysrhythmias usually respond to treatment of acidosis and hyperkalemia
 - use standard drug therapy except Ca channel blockers as they may cause hyperkalemia and cardiac arrest in presence of dantrolene
6. hyperkalemia
 - treat with hyperventilation, bicarbonate, glucose/insulin, calcium
 - bicarb 1-2 mEq/kg IV, calcium chloride 10 mg/kg or calcium gluconate 10-50 mg/kg for life-threatening hyperkalemia and check glucose levels hourly
7. follow ETCO_2 , electrolytes, blood gases, CK, core temperature, urine output and colour with Foley catheter, coagulation studies
 - if CK and/or potassium rises more than transiently or urine output falls to less than 0.5 ml/kg/hr, induce diuresis to >1 ml/kg/hr urine to avoid myoglobinuric renal failure
8. maintain anesthesia with benzodiazepines, opioid, and propofol
9. transfer to ICU bed

Common Medications

Table 11. Intravenous Induction Agents

	Propofol (Diprivan®)	Thiopental (Pentothal®, sodium thiopental, sodium thiopentone)	Ketamine (Ketalar®, Ketaject®)	Benzodiazepines [midazolam (Versed®), diazepam (Valium®), lorazepam (Ativan®)]
Class	• Alkylphenol – hypnotic	• Ultra-short acting thiobarbiturate – hypnotic	• Phencyclidine (PCP) derivative – dissociative	• Benzodiazepines
Action	• Inhibitory at GABA synapse • Decreased cerebral metabolic rate + blood flow, decreased ICP, decreased SVR, decreased BP, and decreased SV	• Decreased time Cl channels open facilitating GABA and suppressing glutamic acid • Decreased cerebral metabolism + decreased blood flow, decreased CPP, decreased CO, decreased BP, decreased reflex tachycardia, decreased respiration	• May act on NMDA, opiate and other receptors • Increased HR, increased BP, increased SVR, increased coronary flow, increased myocardial O_2 uptake, CNS + respiratory depression, bronchial smooth muscle relaxation	• Causes increased glycine inhibitory neurotransmitter, facilitates GABA • Produces antianxiety and skeletal muscle relaxant effects • Minimal cardiac depression
Indications	• Induction • Maintenance • Total intravenous anesthesia (TIVA)	• Induction • Control of convulsive states	• Major trauma, hypovolemia, severe asthma because sympathomimetic	• Used for sedation, amnesia and anxiolysis
Caution	• Allergy (egg, soy) • Pts who cannot tolerate sudden decreased BP (i.e. fixed cardiac output or shock)	• Allergy to barbiturates • Uncontrolled hypotension, shock, cardiac failure • Porphyria, liver disease, status asthmaticus, myxedema	• Ketamine allergy • TCA medication (interaction causes HTN and dysrhythmias) • History of psychosis • Pt cannot tolerate HTN (e.g. CHF, increased ICP, aneurysm)	• Marked respiratory depression
Dosing	• IV induction: 2.5-3.0 mg/kg (less with opioids or premeds) TIVA • Unconscious <1 min • Lasts 4-6 min • $t_{1/2}=0.9$ hrs • Decreased post-op sedation, recovery time, N/V	• IV induction: 3-5 mg/kg TIVA • Unconscious about 30s • Lasts 5 min • Accumulation with repeat dosing – not for maintenance • $t_{1/2}=5-12$ hrs • Post-op sedation lasts hours	• IV induction 1-2 mg/kg • Dissociation in 15s, analgesia, amnesia and unconsciousness in 45-60s • Unconscious for 10-15 min, analgesia for 40 min, amnesia for 1-2 hrs • $t_{1/2} = \sim 3$ hrs	• Onset less than 5 minutes if given IV • Duration of action long but variable/somewhat unpredictable
Special Considerations	• 0-30% decreased BP due to vasodilation • Reduce burning at IV site by mixing with lidocaine	• Combining with rocuronium causes precipitates to form	• High incidence of emergence reactions (vivid dreaming, out-of-body sensation, illusions) • Pretreat with glycopyrrolate to decrease salivation	• Antagonist: flumazenil (Anexate®) competitive inhibitor, 0.2 mg IV over 15s, repeat with 0.1 mg/min (max of 2 mg), $t_{1/2}$ of 60 minutes • Midazolam also has amnestic (antegrade) effect + decreased risk of thrombophlebitis

Table 12. Opioids

Agent	Infusion Rate	PCA Dose	PCA Lockout Interval	
Morphine	0.3-0.9 mg/h	0.2-0.3 mg	30 minutes	
Fentanyl	25-50 µg/h	20-30 µg	15 minutes	
Hydromorphone	0.1-0.2 mg/h	0.15 µg	30 minutes	

Agent	Moderate Dose (IV)	Onset	Duration	Special Considerations
Morphine	0.2-0.3 mg/kg	Moderate (5-10 min)	Moderate (4-5 h)	Histamine release leading to decrease in BP
Meperidine (Demerol®)	2-3 mg/kg	Moderate (10 min)	Moderate (2-4 h)	Anticholinergic, hallucinations, less pupillary constriction than morphine, metabolite build up may cause seizures
Codeine	0.5-1 mg/kg (no IV)	Late (30-60 min)	Moderate (4-6 h)	Primarily post-operative use, not for IV use
Hydromorphone (Dilaudid®)	30-80 µg/kg	Moderate (15 min)	Moderate (4-5 h)	
Fentanyl	3-10 µg/kg	Rapid (<5 min)	Short (0.5-1 h)	Transient muscle rigidity in very high doses
Remifentanyl	0.5-1.5 µg/kg	Rapid (1-3 min)	Ultra short (<10 min)	Only use during induction and maintenance of anesthesia

In general, parenteral route is 2-3 times more potent than oral.

Table 13. Volatile Inhalational Agents

	Sevoflurane	Desflurane	Isoflurane	Enflurane	Halothane	Nitrous oxide (N ₂ O)*
MAC	2.0	6.0	1.2	1.7	0.8	104 (% gas in O ₂)
CNS	Increased ICP	Increased ICP	Decreased cerebral metabolic rate Increased ICP	ECG seizure-like activity, increased ICP	Increased ICP and CBF	—
Resp	Respiratory depression (severely decreased TV, increased RR), decreased response to respiratory CO ₂ reflexes, bronchodilation					—
CVS	Less decrease of contractility, stable HR	Tachycardia with rapid increase in concentration	Decreased BP and CO, increased HR, theoretical chance of coronary steal**	Stable HR, decreased contractility	Decreased BP, CO, HR and conduction Sensitizes myocardium to epinephrine-induced arrhythmias	Can cause decreased HR in pediatric cases in those with existing heart disease
MSK	Muscle relaxation, potentiation of other muscle relaxants, uterine relaxation					

*Properties and Adverse Effects of N₂O

Due to its high MAC, nitrous oxide is combined with other anesthetic gases to attain surgical anesthesia. A MAC of 104% is possible in a pressurized chamber only.

Second Gas Effect: see Determinants of Speed of Onset of Volatile Anesthetics sidebar, A6.

Expansion of closed spaces: closed spaces such as a pneumothorax, the middle ear, bowel lumen and ETT cuff will markedly enlarge if N₂O is administered.

Diffusion hypoxia: During anesthesia, the washout of N₂O from body stores into alveoli can dilute the alveolar [O₂], creating a hypoxic mixture if the original [O₂] is low.

**Coronary Steal: N₂O causes small vessel dilation which may compromise blood flow to poorly perfused areas of heart.

Table 14. Depolarizing Muscle Relaxants (Non-Competitive): Succinylcholine (SCh)

Mechanism of Action	Mimics ACh and binds to ACh receptors causing prolonged depolarization; initial fasciculation may be seen, followed by temporary paralysis secondary to blocked ACh receptors by SCh
Intubating Dose	1-2 mg/kg
Onset	30-60 seconds – RAPID (fastest of all muscle relaxants)
Duration	5-10 minutes – SHORT (no reversing agent for SCh)
Metabolism	SCh is hydrolyzed by plasma cholinesterase (pseudocholinesterase), found only in plasma and not at the NMJ
Indications	<ul style="list-style-type: none"> • Assist intubation • Increased risk of aspiration (need rapid paralysis and airway control) • Short procedures (e.g. full stomach), DM, hiatus hernia, obesity, pregnancy, trauma • Electroconvulsive therapy (ECT) • Laryngospasm
Side Effects	<ol style="list-style-type: none"> 1. SCh also stimulates muscarinic cholinergic autonomic receptors (in addition to nicotinic receptors) <ul style="list-style-type: none"> • May cause bradycardia, dysrhythmias, sinus arrest, increased secretions of salivary glands (especially in children) 2. Hyperkalemia <ul style="list-style-type: none"> • Disruption of motor nerve activity causes proliferation of extrajunctional (outside NMJ) cholinergic receptors • Depolarization of an increased number of receptors by SCh may lead to massive release of potassium out of muscle cells • Patients at risk: <ul style="list-style-type: none"> • 3rd degree burns 24 hrs-6 mths after injury • Traumatic paralysis or neuromuscular diseases (e.g. muscular dystrophy) • Severe intra-abdominal infections • Severe closed head injury • Upper motor neuron lesions 3. Can trigger malignant hyperthermia (MH) 4. Increase ICP/intraocular pressure (IOP)/intra gastric pressure (no increased risk of aspiration if competent lower esophageal sphincter) 5. Fasciculations, post-op myalgia – may be minimized if small dose of non-depolarizing agent given before SCh administration
Contraindications	
Absolute	Known hypersensitivity or allergy, positive history of malignant hyperthermia, myotonia (m. congenita, m. dystrophica, paramyotonia congenita), high risk for hyperkalemic response
Relative	Known history of plasma cholinesterase deficiency, myasthenia gravis, myasthenic syndrome, familial periodic paralysis, open eye injury

Table 15. Non-Depolarizing Muscle Relaxants (Competitive)

Mechanism of Action	Competitive blockade of postsynaptic ACh receptors preventing depolarization					
Classification	Short	Intermediate			Long	
	Mivacurium	Rocuronium	Vecuronium	Cisatracurium	Pancuronium	Doxacurium
Intubating Dose (mg/kg)	0.2	0.6	0.1	0.1	0.1	0.05
Onset (min)	2-3	1.5	2-3	3	3-5	5-7
Duration (min)	15-25	30-45	45-60	40-60	90-120	90-120
Metabolism	Plasma cholinesterase	Liver (major) Renal (minor)	Liver	Hofmann Eliminations	Renal (major) Liver (minor)	Renal
Indications	Assist intubation, assist mechanical ventilation in some ICU patients, reduce fasciculations and post-op myalgias secondary to SCh					
Side Effects						
Histamine Release	Yes	No	No	No	No	Yes
Other	—	—	—	—	Tachycardia	—
Considerations	Increased duration of action in renal or liver failure	Quick onset of rocuronium allows its use in rapid sequence induction Cisatracurium is good for patients with renal or hepatic insufficiency			Pancuronium if increased HR and BP desired, doxacurium if cardiovascular stability needed	

Table 16. Reversal Agents for Non-Depolarizing Relaxants

Cholinesterase Inhibitor	Neostigmine	Pyridostigmine	Edrophonium
Onset and Duration	Intermediate	Longest	Shortest
Mechanism of Action	Inhibits enzymatic degradation of ACh, increases ACh at nicotinic and muscarinic receptors, displaces non-depolarizing muscle relaxants Muscarinic effects of reversing agents include unwanted bradycardia, salivation and increased bowel peristalsis*		
Dose	0.04-0.08 mg/kg	0.1-0.4 mg/kg	0.5-1 mg/kg
Recommended Anticholinergic	Glycopyrrolate	Glycopyrrolate	Atropine
Dose of Anticholinergic per mg	0.2 mg	0.05 mg	0.014 mg

*Atropine and glycopyrrolate are anticholinergic agents administered during the administration of reversal agents to minimize muscarinic effects

Table 17. Local Anesthetic Agents

	Max. Dose	Max. Dose with Epinephrine	Potency	Duration
chlorprocaine	11 mg/kg	14 mg/kg	Low	15-30 min
lidocaine	5 mg/kg	7 mg/kg	Medium	1-2 hours
bupivacaine	2.5 mg/kg	3 mg/kg	High	3-8 hours

References

- Barash PG, Cullen BF, Stoelting RK. (2001). Clinical anesthesia, 4th Edition. Philadelphia, PA: Lippincott Williams and Wilkins.
- Blanc VF, Tremblay NA. The complications of tracheal intubation: a new classification with review of the literature. *Anesthesia & Analgesia* 1974; 53: 202-213.
- Carlisle J, Stevenson CA. Drugs for preventing post-operative nausea and vomiting. *Cochrane Database of Systematic Reviews* 2006, Issue 3.
- Collins VJ. (1996). Physiologic and pharmacologic bases of anesthesia. Philadelphia, PA: Lippincott Williams and Wilkins.
- Craft TM, Upton PM. (2001). Key topics in anesthesia, clinical aspects, 3rd Edition. Oxford, UK: BIOS Scientific Publishers Ltd.
- Duke J. (2010). Anesthesia Secrets, 4th Edition. Philadelphia, PA: Mosby, Inc.
- Eagle KA, Berger PB, Calkins H et al. ACC/AHA Guideline update for perioperative cardiovascular evaluation for noncardiac surgery - executive summary. *Circulation* 2002; 105:1257-1267.
- Ezekiel MR. (2001). Handbook of anesthesiology, 2002-2003 Edition. Philadelphia, PA: Current Clinical Strategies Publishing.
- Frank SM, Fleisher LA, Breslow MJ et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: A randomized clinical trial. *JAMA* 1997; 277:1127-1134.
- Hebert PC, Wells G, Blajchman MA et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *New England Journal of Medicine* 1999; 340:409-417.
- Henderson JJ, Popat MT, Latto IP, Pearce AC. Difficult Airway Society Guidelines for management of the unanticipated difficult intubation. *Anaesthesia* 2004; 59:675-694.
- Hudcova J, McNicol ED, Quah CS et al. Patient controlled opioid analgesia versus conventional opioid analgesia for post-operative pain. *Cochrane Database of Systematic Reviews* 2006; Issue 4.
- Hurford WE, Bailin MT, Davison JK et al (Eds). (2002). Clinical anesthesia procedures of the Massachusetts General Hospital, sixth edition. Philadelphia, PA: Lippincott Williams and Wilkins.
- Hwang, NC. (1998). Anaesthesia: A practical handbook. Singapore: Oxford University Press.
- Kalant H, Roschlau WH (Eds). (1998). Principles of medical pharmacology. New York, NY: Oxford University Press.
- Lawrence PF. (2000). Anesthesiology. In Essentials surgical specialties (pgs 1-67). Philadelphia, PA: Lippincott Williams and Wilkins.
- Lee A, Fan LTY. Stimulation of the wrist acupuncture point P6 for preventing post-operative nausea and vomiting. *Cochrane Database of Systematic Reviews* 2009; Issue 2.
- Lette J, Waters D, Bernier H et al. Preoperative and long-term cardiac risk assessment predictive value of 23 clinical descriptors, 7 multivariate scoring systems, and quantitative dipyridamole imaging in 360 patients. *Annals of Surgery* 1992; 216:192-204.
- Malignant Hyperthermia Association of the United States Website. Last accessed on September 26th 2010. Retrieved from <<http://www.mhausa.org>>.
- Mangano DT, London MJ, Browner WS et al. Long-term cardiac prognosis following noncardiac surgery. *Journal of the American Medical Association* 1992; 268:233-240.
- Mangano DT, Layug EL, Wallace A, Tateo MS. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *New England Journal of Medicine* 1996; 335:1713-1720.
- Merchant R, Bosenberg C, Brown K et al. Guidelines to the practice of anesthesia revised 2010 edition. *Canadian Journal of Anesthesia* 2010; 57:58-87.
- Miller RD. (2000). Anesthesia, 5th edition. Philadelphia, PA: Churchill Livingstone, Inc.
- Morgan GE, Mikhail MS, Murray MJ. (2002). Clinical anesthesiology, 4th edition. New York, NY: McGraw-Hill Medical.
- Palda VA, Detksy AS. Perioperative assessment and management of risk from coronary artery disease. *Annals of Internal Medicine* 1997; 127:313-328.
- Perel P, Roberts I, Pearson M. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database of Systematic Reviews* 2007; Issue 4.
- Poldermans D, Boersma E, Bax JJ et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *New England Journal of Medicine* 1999; 341:1789-1794.
- Posner KL, Van Norman GA, Chan V. Adverse cardiac outcomes after noncardiac surgery in patients with prior percutaneous transluminal coronary angioplasty. *Anesthesia & Analgesia* 1999; 89:553-560.
- Rao TL, Jacobs KH, El-Etr AA. Reinfarction following anaesthesia in patients with myocardial infarction. *Anaesthesiology* 1983; 59: 499-505.
- Roberts JR, Spadafora M, Cone DC. Proper depth placement of oral endotracheal tubes in adults prior to radiographic confirmation. *Academic Emergency Medicine* 1995;20-24.
- Rodgers A, Walker N, Schug S et al. Reduction of post-operative mortality and morbidity with epidural or spinal anesthesia: results from overview of randomized trials. *British Medical Journal* 2000; 321:1-12.
- Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective beta-blockers for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2005; Issue 4.
- Salpeter SR, Ormiston TM, Salpeter EE, Wood-Baker. Cardioselective beta-blockers for reversible airway disease. *Cochrane Database of Systematic Reviews* 2002; Issue 4.
- Sessler DI. Complications and treatment of mild hypothermia. *Anesthesiology* 2001; 95:531-543.
- Sullivan P. (1999). Anesthesia for medical students. Ottawa, Ontario, Canada: Doculink International.
- Zwilling CW, Pierson DJ, Creagh CE et al. Complications of assisted ventilation. *American Journal of Medicine* 1974; 57:161-9.

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Off Pump Coronary Artery Bypass (OPCAB) Surgery			

Basic Anatomy Review



Coronary Circulation

- conventional arterial supply to the heart arises from the right and left coronary arteries, originating from the root of the aorta (see Figure 1)
 - right coronary artery (RCA)
 - ♦ acute marginal branches
 - ♦ atrioventricular (AV) nodal artery
 - ♦ posterior interventricular artery (PIV) = posterior descending artery (PD)
 - left main coronary artery (LCA): two major branches
 - ♦ left anterior descending artery (LAD)
 - septal branches
 - diagonal branches
 - ♦ left circumflex artery (LCx)
 - obtuse marginal branches
- dominance of circulation
 - right-dominant circulation: PIV and at least one posterolateral branch arise from RCA (80%)
 - left-dominant circulation: PIV and at least one posterolateral branch arise from LCx (15%)
 - balanced circulation: dual supply of posteroinferior LV from RCA and LCx (5%)
- the sinoatrial (SA) node is supplied by the SA nodal artery, which may arise from the RCA (60%) or LCA (40%)
- most venous blood from the heart drains into the RA through the coronary sinus, although a small amount drains through Thebesian veins into all four chambers, contributing to the physiologic R-L shunt

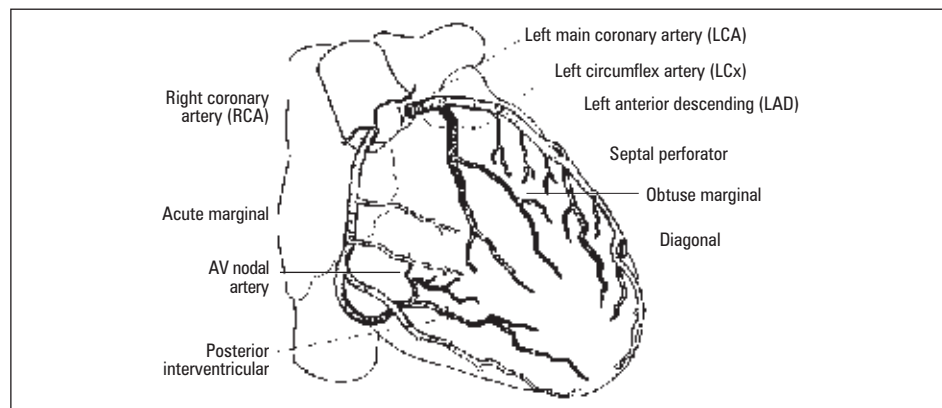


Figure 1. Anatomy of the Coronary Arteries (right anterior oblique projection)

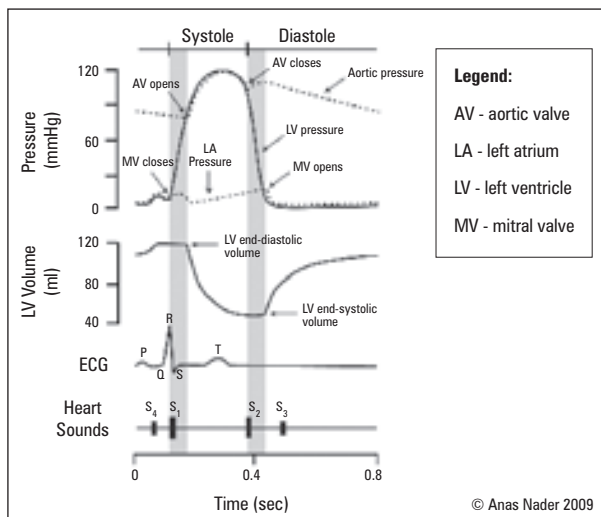


Figure 2a. Cardiac Cycle

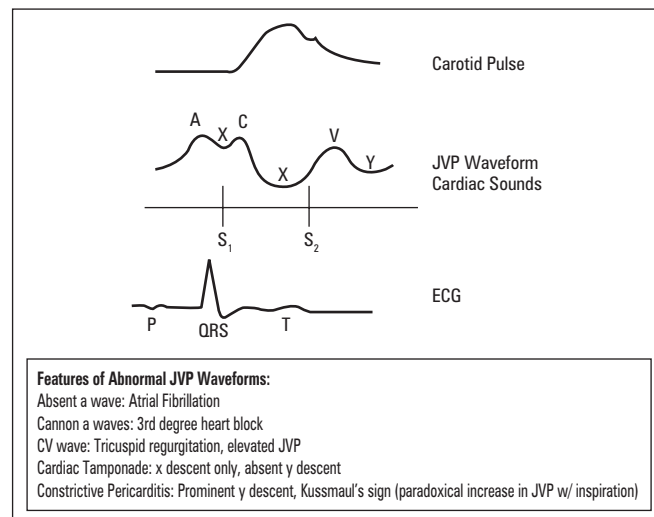
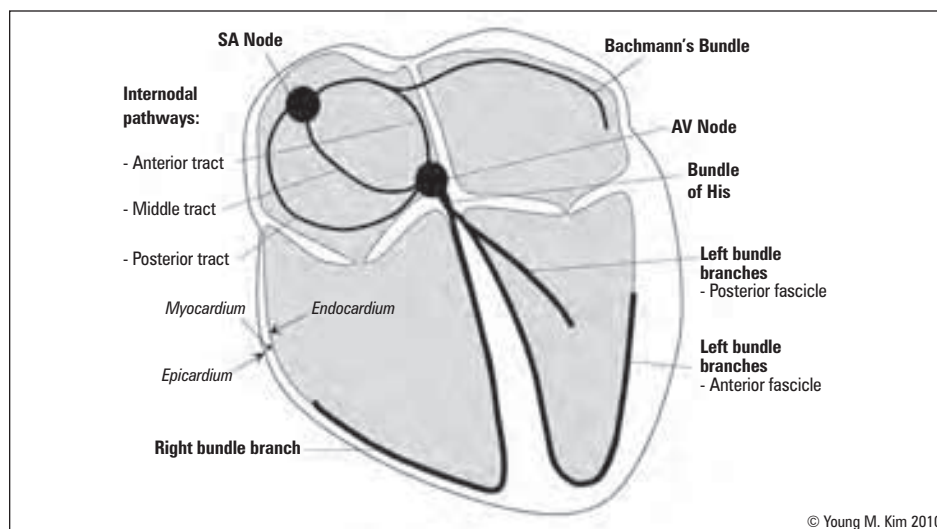


Figure 2b. Cardiac Cycle, JVP Pulse and Carotid Pulse

Cardiac Anatomy



- **layers of the heart**
 - endocardium
 - myocardium
 - epicardium = visceral pericardium
 - pericardial space
 - parietal pericardium
- **valves**
 - tricuspid valve (TV): separates RA and RV
 - pulmonic valve (PV): separates RV and pulmonary artery (PA)
 - mitral valve (MV): separates LA and LV
 - aortic valve (AV): separates LV and ascending aorta
- **conduction system**
 - impulses travel from: SA node → AV node → bundle of His → LBB/RBB → Purkinje fibres
 - SA node governs pacemaking control
 - anterior-, middle- and posterior-internal nodal tracts carry impulses in the right atrium and along Bachmann's bundle in the left atrium
 - atrial impulses converge at the AV node
 - ♦ the AV node is the only conducting tract from the atria to the ventricles because of electrical isolation by the annulus fibrosis (except when accessory pathways are present)
 - the bundle of His bifurcates into left and right bundle branches (LBB and RBB)
 - LBB further splits into anterior and posterior fascicles
 - RBB and fascicles of LBB give off Purkinje fibres which conduct impulses into the ventricular myocardium
- **cardiovascular innervation**
 - **sympathetic nerves**
 - ♦ innervate the sinoatrial node (SAN), atroventricular node (AVN), ventricular myocardium and vasculature
 - ♦ SAN (β_1) fibres increase pacemaking activity (chronotropy)
 - ♦ cardiac muscle (β_1) fibres increase contractility (inotropy) to help increase cardiac output
 - ♦ stimulation of β_1 - and β_2 -receptors in the skeletal and coronary circulation causes vasodilatation
 - **parasympathetic nerves**
 - ♦ innervate the SAN, AVN, atrial myocardium but few vascular beds
 - ♦ basal vagal tone dominates the tonic sympathetic stimulation of the SAN and AVN resulting in slowing of pacemaking activity and conduction (i.e. reduced chronotropy and dromotropy)
 - ♦ parasympathetics have very little impact on total peripheral vascular resistance



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Figure 3. Conduction System of the Heart

Differential Diagnoses of Common Presentations

Note: **bold** text indicates most common, underlined text indicates life threatening

Chest Pain

- Pulmonary
 - **pneumonia**
 - pulmonary embolism (PE)
 - pneumothorax/hemothorax, tension pneumothorax
 - empyema
 - pulmonary neoplasm
 - bronchiectasis
 - TB
- Cardiac
 - MI/angina
 - myocarditis
 - pericarditis/Dressler's syndrome
 - cardiac tamponade
- Gastrointestinal
 - esophageal: spasm, **GERD**, esophagitis, ulceration, achalasia, neoplasm, Mallory-Weiss syndrome
 - PUD
 - gastritis
 - pancreatitis
 - biliary colic
- Mediastinal
 - lymphoma
 - thymoma
- Vascular
 - dissecting aortic aneurysm
- Surface structures
 - costochondritis
 - rib fracture
 - skin (bruising, shingles)
 - breast

Syncope

- Hypovolemia
- Cardiac
 - structural or obstructive causes
 - ♦ myocardial disease (e.g. acute coronary syndrome)
 - ♦ aortic stenosis
 - ♦ hypertrophic cardiomyopathy (HCM)
 - ♦ cardiac tamponade/constrictive pericarditis
 - arrhythmias (see arrhythmia section)
- Respiratory
 - massive PE
 - pulmonary hypertension
 - hypoxia
 - hypercapnia
- Neurologic
 - stroke/TIA (esp. vertebrobasilar insufficiency)
 - migraine
 - seizure
 - **vasovagal**
- Metabolic
 - **anemia**
 - **hypoglycemia**
- Drugs
 - antihypertensives
 - antiarrhythmics
 - beta-blockers, CCBs
- Psychiatric
 - panic attack

Local Edema

- Inflammation/infection
- Venous or lymphatic obstruction
 - thrombophlebitis/deep vein thrombosis
 - chronic lymphangitis
 - venous insufficiency
 - filariasis

Generalized Edema

- Increased hydrostatic pressure
 - increased fluid retention
 - ♦ cardiac causes e.g. CHF
 - ♦ hepatic causes e.g. cirrhosis
 - ♦ renal causes e.g. acute and chronic renal failure
 - vasodilators (especially CCBs)
 - refeeding edema
- Decreased oncotic pressure
 - hypoalbuminemia
- Hormonal
 - hypothyroidism
 - exogenous steroids
 - pregnancy
 - estrogens

Palpitations

- Cardiac
 - **arrhythmias** (PAC, PVC, SVT, VT)
 - mitral valve prolapse
 - valvular heart disease
 - hypertrophic obstructive cardiomyopathy
- Endocrine
 - thyrotoxicosis
 - pheochromocytoma
 - hypoglycemia
- Systemic
 - fever
 - anemia
- Drugs
 - tobacco, caffeine, alcohol, epinephrine, ephedrine, aminophylline, atropine
- Psychiatric
 - panic attack

Dyspnea

- Cardiovascular
 - acute MI
 - **CHF/LV failure**
 - aortic stenosis/mitral stenosis
 - cardiac tamponade
 - elevated pulmonary venous pressure
- Respiratory
 - airway disease
 - ♦ **asthma**
 - ♦ COPD exacerbation
 - ♦ upper airway obstruction (anaphylaxis, foreign body, mucus plugging)
 - parenchymal lung disease
 - ♦ ARDS
 - ♦ pneumonia
 - ♦ interstitial lung disease
 - pulmonary vascular disease
 - ♦ pulmonary embolism
 - ♦ pulmonary HTN
 - ♦ pulmonary vasculitis
 - pleural disease
 - ♦ pneumothorax
 - pleural effusion
- Neuromuscular and chest wall disorders
 - C-spine injury
 - polymyositis, myasthenia gravis, Guillain-Barré syndrome
 - kyphoscoliosis
- Anxiety/psychosomatic
- Severe anemia

Cardiac Diagnostic Tests

Electrocardiography (ECG) Basics

- the electrocardiogram (ECG) is a graphic representation of the electrical activity of the heart recorded from the surface of the body
- on the ECG graph
 - the horizontal axis represents time
 - 1 mm (1 small square) = 40 msec
 - 5 mm (1 large square) = 200 msec (at paper speed 25 mm/sec)
 - the vertical axis represents voltage
 - 1 mm (1 small square) = 0.1 mV
 - 10 mm (2 large squares) = 1 mV (at standard gain setting)
- leads
 - standard 12-lead ECG
 - limb leads: I, II, III, aVL, aVR, aVF
 - precordial leads: V1-V6 (V1-V2 septal, V3-V4 anterior, V5-V6 lateral)
 - additional leads
 - right-sided leads: V3R-V6R (useful in RV infarction and dextrocardia)
 - lateral = I, aVL, V5, V6; inferior = II, III, aVF; frontal = V1-V4

Overview of Diagnostic Tests

- Cardiac biomarkers (Tn, CK-MB) – in symptomatic state
- ECG – at rest, with stress, or in symptomatic state
- Echocardiography – at rest, or with stress
- Nuclear imaging – with stress
- Angiography (cardiac catheterization)
- CTA
- MRA/MRI

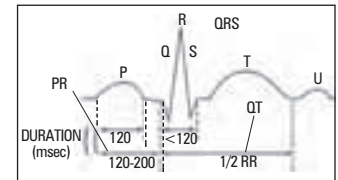


Figure 4. ECG Waveforms and Normal Values

Approach to ECGs

Rate

- normal = 60-100 bpm (atrial rate: 150-250 bpm = paroxysmal tachycardia, 250-350 bpm = atrial flutter, >350 bpm = atrial fibrillation)
- regular rhythm
 - to calculate the rate, divide 300 by number of large squares between 2 QRS complexes (there are 300 large squares in 1 minute: 300 x 200 msec = 60 sec)
 - or remember 300-150-100-75-60-50-43 (rate falls in this sequence with the number of additional large squares between QRS)
- irregular rhythm
 - rate = 6 x number of R-R intervals in 10 seconds (the "rhythm strips" are 10 second recordings)
 - types: wandering pacemaker, multifocal atrial tachycardia, atrial fibrillation
- atrial escape = 60-80 bpm; junctional escape = 40-60 bpm; ventricular escape = 20-40 bpm

Rhythm

- regular = R-R interval is the same across the tracing
- irregular = R-R interval varies across the tracing
 - regularly-irregular = repeating pattern of varying R-R intervals
 - irregularly irregular = R-R intervals vary erratically
- normal sinus rhythm (NSR)
 - P wave precedes each QRS; QRS follows each P wave
 - P wave axis is normal (positive in leads I, aVF)
 - rate between 60-100 bpm

Axis

- mean axis indicates the direction of the mean vector
- can be determined for any waveform (P, QRS, T)
- the standard ECG reported QRS axis usually refers to the mean axis of the frontal plane; it indicates the mean direction of ventricular depolarization forces
- QRS axis in the horizontal plane is not routinely calculated; it is directed posteriorly and to the left
 - the transition from negative to positive is usually in lead V3
- QRS axis in the frontal plane (see Figure 5)
 - normal axis: -30° to 90° (i.e. positive QRS in leads I and II)
 - left axis deviation (LAD): axis < -30°
 - right axis deviation (RAD): axis > 90°



Rate Calculations

- Examples
- Practice



Approach to ECGs Summary

- Rate
- Rhythm
- Axis
- Conduction
- Chamber enlargement/hypertrophy
- Ischemia/infarction
- Miscellaneous



For more examples and practice, visit www.ecgmadesimple.com.

Differential Diagnosis for Left and Right Axis Deviation

LAD	RAD
Left Ant. Hemiblock	RVH
Inferior MI	Left Post. Hemiblock
WPW	PE
RV Pacing	COPD
Normal Variant	Lateral MI
Elevated Diaphragm	WPW
Lead Misplacement	Dextrocardia
Endocardial cushion defect	Septal Defects

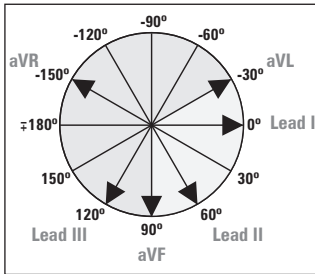


Figure 5. Axial Reference System

Each lead contains a (+) area displayed by the bold arrows. Impulses traveling toward the positive region of the lead results in an upward deflection in that lead. Normal QRS axis is between -30° and $+90^\circ$.

Intraventricular Conduction Abnormalities

Right Bundle Branch Block (RBBB)

Complete RBBB

- QRS duration >120 msec
- Positive QRS in lead V1 (rSR' or occasionally broad R wave)
- Broad S waves in leads I, V5-6 (>40 msec)
- Usually secondary T wave inversion in leads V1-2

Left Bundle Branch Block (LBBB)

Complete LBBB

- QRS duration >120 msec
- Broad notched or slurred R waves in leads I, aVL and usually V5 and V6
- Deep broad S waves in leads V1-2
- Secondary ST-T changes (-ve in leads with broad R waves, +ve in V1-2) are usually present
- LBBB usually masks ECG signs of myocardial infarction

Left Anterior Fascicular Block (LAFB) (Left Anterior Hemiblock)

- Left axis deviation (-30° to -90°)
 - Small q and prominent R in leads I and aVL
 - Small r and prominent S in leads II, III, and aVF

Left Posterior Fascicular Block (LPFB) (Left Posterior Hemiblock)

- Right axis deviation (110° to 180°)
 - Small r and prominent S in leads I and aVL
 - Small q and prominent R in leads II, III, and aVF

Bifascicular Block

- RBBB pattern
 - Small q and prominent R
- The first 60 msec (1.5 small squares) of the QRS shows the pattern of LAFB or LPFB
- Bifascicular block refers to impaired conduction in two of the three fascicles, most commonly a RBBB and left anterior hemiblock; the appearance on an ECG meets the criteria for both types of blocks

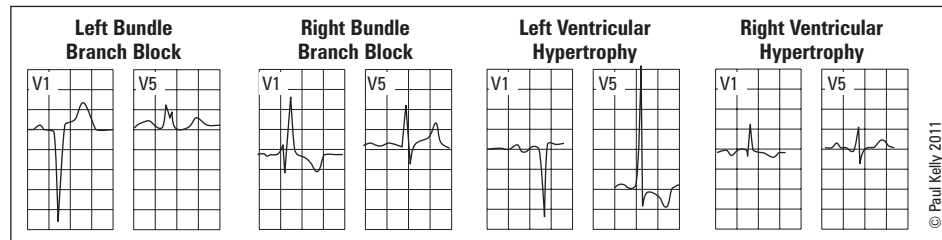


Figure 6. Complete LBBB, RBBB, LVH and RVH (only samples, please see online examples for the full range of waveforms and the text for additional characteristics)

Nonspecific Intraventricular Block

- QRS duration >120 msec
- absence of criteria for LBBB or RBBB

Hypertrophy and Chamber Enlargement

- left ventricular hypertrophy (LVH)
 - S in V1 + R in V5 or V6 >35 mm above age 40, (>40 mm for age 31-40, >45 mm for age 21-30)
 - R in aVL >11 mm
 - R in I + S in III >25 mm
 - additional criteria:
 - ♦ LV strain pattern (ST depression and T wave inversion in leads I, aVL, V4-V6)
 - ♦ left atrial enlargement
- right ventricular hypertrophy (RVH)
 - right axis deviation
 - R/S ratio >1 or qR in lead V1
 - RV strain pattern: ST segment depression and T wave inversion in leads V1-2
- left atrial enlargement (LAE)
 - biphasic P wave with the negative terminal component of the P wave in lead V1 ≥ 1 mm wide and ≥ 1 mm deep
 - P wave >120 msec, notched in lead II ("P mitrale")
- right atrial enlargement (RAE)
 - P wave >2.5 mm in height in leads II, III, or aVF ("P pulmonale")

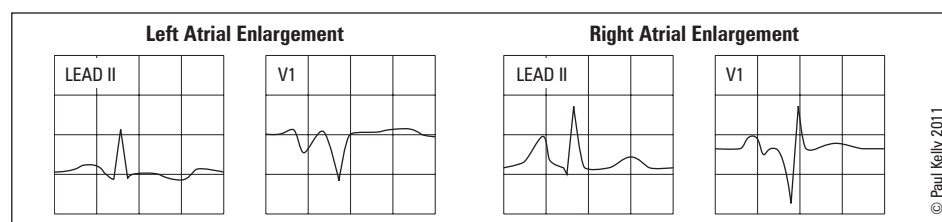


Figure 7. LAE, RAE (only samples, please see online examples and text above for characteristics)

Ischemia/Infarction

- look for the anatomic distribution of the following ECG abnormalities (see Table 1)
- ischemia
 - ST segment depression
 - T wave inversion (most commonly in V1-V6)
- injury
 - transmural (involving the epicardium) – ST elevation in the leads facing the area injured/infarcted; transient ST elevation may occur in patients with coronary artery spasm (e.g. Prinzmetal angina) can be slight or prominent (>10 mm)
 - subendocardial – marked ST depression in the leads facing the affected area; it may be accompanied by enzyme changes and other signs of myocardial infarction; may also occur with angina

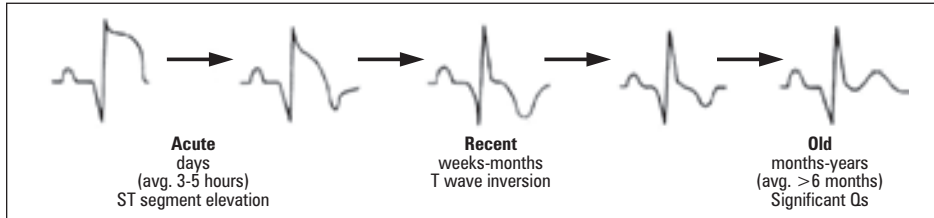


Figure 8. ECG Changes with Infarction

- evolving infarction (ST elevation in contiguous leads = acute MI)
- “typical” sequential changes of evolving myocardial infarction
 - 1st
 - ♦ hyperacute T waves (tall, symmetric T waves) in the leads facing the infarcted area, with or without ST elevation
 - 2nd
 - ♦ ST elevation (injury pattern) in the leads facing the infarcted area
 - ♦ usually in the first hours post infarct
 - ♦ in acute posterior infarction, there is ST depression in V1-V3 (reciprocal to ST elevation in the posterior leads, that are not recorded in the standard 12-lead ECG)
 - 3rd
 - ♦ significant Q waves: >40 msec or >1/3 of the total QRS (hours to days post-infarct)
 - 4th
 - ♦ inverted T waves (one day to weeks after infarction)
 - this classical sequence, however, does not always occur, e.g.
 - ♦ Q waves of infarction may appear in the very early stages, with or without ST changes
 - ♦ non-Q wave infarction: there may be only ST or T changes, despite clinical evidence of infarction
- completed infarction
 - abnormal Q waves (note that wide Q waves may be found in III and aVL in normal individuals)
 - ♦ duration >40 msec (>30 msec in aVF for inferior infarction)
 - ♦ Q/QRS voltage ratio is >33%
 - abnormal R waves (R/S ratio >1, duration >40 msec) in V1 and more frequently in V2 are found in posterior infarction (usually in association with signs of inferior and/or lateral infarction)



Significant ECG Changes

- Look for ST changes starting at 80 msec from J point
- J point = the junction between the QRS complex and the ST segment
- ST elevation: at least 1mm in 2 adjacent limb leads, or at least 1-2 mm in adjacent precordial leads
- ST depression: downsloping or horizontal
- Q wave: pathological if QRS ≥ 1 small square (≥ 40 msec) or >33% of the total QRS



Insignificant Q wave

Septal depolarization by the left bundle
Seen in leads I, II, III, aVL, V5, V6
<40 msec



Differential of ST Segment Changes

• ST Elevation

- Acute STEMI
- Ventricular Aneurysm
- LBBB
- Acute Pericarditis (diffuse changes)
- Ischemia w/reciprocal changes
- Post-MI
- Vasospastic (Prinzmetal's) angina
- Hypothermia (Osborne waves)
- Early repolarization (Normal variant; need old ECG's)

• ST Depression

- Acute NSTEMI or ischemia
- LVH or RVH with strain
- Post-MI
- STEMI with reciprocal changes
- Left or Right BBB
- Wolff-Parkinson-White syndrome

Table 1. Areas of Infarction(Q wave)/Ischemia (right dominant anatomy)

Vessel Usually Involved	Infarct Area (LAD and Circ)	Leads (LAD and Circ)
Left anterior descending (LAD)	Anteroseptal	V1, V2
	Anterior	V3, V4
	Anterolateral	I, aVL, V3-6
	Extensive anterior	I, aVL, V1-6
Right coronary artery (RCA)	Inferior	II, III, aVF
	Right ventricle	V3R, V4R (right sided chest leads)
	Posterior MI (assoc. with inf. MI)	V1, V2 (prominent R waves)
Circumflex	Lateral	I, aVL, V5-6
	Isolated posterior MI	V1, V2 (prominent R waves)

MISCELLANEOUS ECG CHANGES

Electrolyte Disturbances

- hyperkalemia (see Figure 9)
 - mild to moderate (K 5-7 mmol/L): tall peaked T waves
 - severe (K >7 mmol/L): progressive changes whereby P waves flatten and disappear, QRS widens and may show bizarre patterns, axis shifts left or right, ST shift with tall T waves
- hypokalemia (see Figure 10)
 - ST segment depression, prolonged QT interval, low T waves, prominent U waves (U>T)
 - enhances the toxic effects of digitalis
- hypercalcemia: shortened QT interval
- hypocalcemia: prolonged QT interval

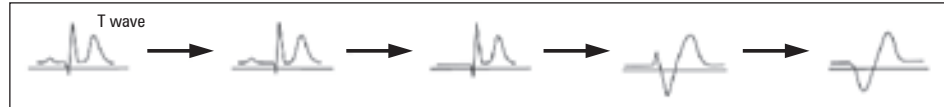


Figure 9. Hyperkalemia (sinusoidal)



Figure 10. Hypokalemia



Low Voltage

- Definition: total QRS height in precordial leads <10 mm and limb leads <5 mm
- Differential diagnosis
 - Myocardial disease
 - ♦ Ischemia
 - ♦ Cardiomyopathy (usually infiltrative type), myocarditis
 - Pericardial effusion
 - Thick chest wall/barrel chest: COPD, obesity
 - Generalized edema
 - Hypothyroidism/myxedema
 - Inappropriate voltage standardization

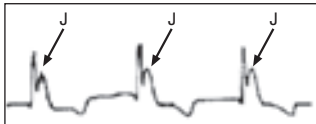


Figure 11. Osborne J Waves of a Hypothermic Patient

Hypothermia

- sinus bradycardia
- when severe, prolonged QRS and QT intervals
- atrial fibrillation with slow ventricular response and other atrial/ventricular dysrhythmias
- Osborne J waves (see Figure 11): “hump-like” waves at the junction of the J point and the ST segment

Pericarditis

- early – diffuse ST segment elevation ± PR segment depression, upright T waves
- later – isoelectric ST segment, flat or inverted T waves
- low voltage if chronic constrictive pericarditis
- tachycardia

Drug Effects

- digitalis
 - therapeutic levels may be associated with “digitalis effect” (see Figure 12):
 - ♦ ST downsloping or “scooping”
 - ♦ T wave depression or inversion
 - ♦ QT shortening ± U waves
 - ♦ slowing of ventricular rate in atrial fibrillation
 - toxic levels associated with:
 - ♦ arrhythmias: paroxysmal atrial tachycardia (PAT) with conduction blocks, severe bradycardia in atrial fibrillation, accelerated junctional rhythms, PVCs, ventricular tachycardia (see *Arrhythmias*, C12)
 - ♦ “regularization” of ventricular rate in atrial fibrillation due to a junctional rhythm and AV dissociation
- amiodarone, quinidine, phenothiazines, tricyclic antidepressants, antipsychotics, some antihistamines, some antibiotics: prolonged QT interval, U waves

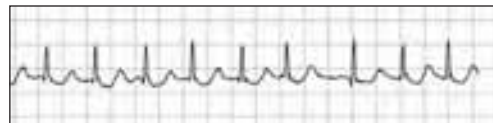


Figure 12. Atrial Fibrillation, ST Change due to Digitalis (“digitalis effect”)



Digitalis Side Effects

Palpitations, fatigue, visual changes (yellow vision), decreased appetite, hallucinations, confusion and depression.



Quinidine

- Wide P wave
- Wide QRS
- Prolonged QT
- ± ST depression
- ± U wave



Pacemakers

- Demand pacemaker has discharge (narrow vertical spike on ECG strip) prior to QRS
- Atrial pacemaker has discharge prior to P wave
- Triggered pacemaker has a discharge following the P wave but prior to the QRS
- Atrial and ventricular pacing have discharged before the P wave and QRS wave

Cardiac Biomarkers

- provide diagnostic and prognostic information and identify increased risk of mortality in acute coronary syndromes

Table 2. Cardiac Enzymes

Enzyme	Peak	Duration Elevated	DDx of Elevation
Troponin I, Troponin T	1-2 days	Up to 2 weeks	MI, CHF, AF, acute pulmonary embolism, myocarditis, chronic renal insufficiency, sepsis, hypovolemia
CK-MB	1 day	3 days	Myocardial infarction, myocarditis, pericarditis, muscular dystrophy, cardiac defibrillation, etc.

- check troponin I at presentation and 8h later \pm creatine kinase-MB (CK-MB, depends on local laboratory protocol)
- new CK-MB elevation can be used to diagnose reinfarction, troponin cannot
- other biomarkers of cardiac disease:
 - AST and LDH also increased in myocardial infarction (low specificity)
 - BNP and NT-proBNP – secreted by ventricles in response to increased end-diastolic pressure and volume
 - DDx: CHF, AF, PE, COPD exacerbation, pulmonary hypertension

Ambulatory ECG

- indications for outpatient management: palpitations, syncope, antiarrhythmic drug monitoring, and arrhythmia surveillance in patients with documented or potentially abnormal rhythms, surveillance of non-sustained arrhythmias that can lead to prophylactic intervention
- available technologies
 - Holter monitor
 - battery operated, continually records up to 3 leads for 24-48 hrs
 - symptoms recorded by patient on Holter clock for correlation with ECG findings
 - continuous loop recorder (diagnostic yield 66-83%)
 - worn continuously and can record data before and after patient activation for symptomatic episodes (usually worn for 2 weeks)
 - external and implantable devices
 - external devices can be transtelephonically downloaded
 - implantable loop recorder (ILR) – implanted subcutaneously to the right or left of the sternum; triggered by placing an activator over it; anterograde and retrograde recording time is programmable; cannot be transtelephonically downloaded; left in place for 14 to 18 months

Echocardiography

Transthoracic Echocardiography (TTE)

- ultrasound beams are directed across the chest wall to obtain images of the heart
- indications: evaluation of left ventricular ejection fraction (LVEF), wall motion abnormalities, myocardial ischemia and complications of MI, chamber sizes, wall thickness, valve morphology, proximal great vessels, pericardial effusion, unexplained hypotension, murmurs, syncope, congenital heart disease
- use with Doppler, which is used to quantify degree of valvular stenosis or regurgitation

Transoesophageal Echocardiography (TEE)

- ultrasound probe inserted into the esophagus to allow for better resolution of the heart and its structures
- better visualization of posterior structures, such as left atrium, mitral and aortic valves, interatrial septum
- invasive procedure, used to complement transthoracic echocardiography
- indications: intracardiac thrombi, tumours, valvular vegetations (infective endocarditis), aortic dissection, aortic atheromas, prosthetic valve function, shunts, technically inadequate transthoracic studies
- use with Doppler, which is used to quantify degree of valvular stenosis or regurgitation

Stress Echocardiography

- echocardiography in combination with either physiologic (exercise treadmill or bike testing) or pharmacologic (dobutamine infusion) stress
- validated in demonstrating myocardial ischemia and assessing viability
- provides information on the global left ventricular response to exercise
- regional wall motion is analyzed at rest and with stress
- used for valvular heart disease evaluation

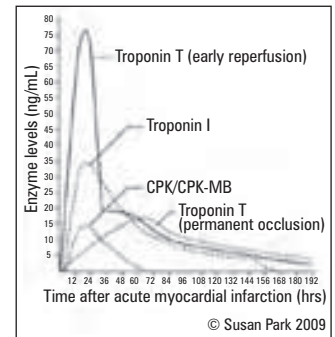


Figure 13. Cardiac Enzymes

Use of B-Type Natriuretic Peptide in the Evaluation and Management of Acute Dyspnea (BASEL)

NEJM 2004; 350:647-54

Study: Prospective, randomized controlled trial.

Population: 452 patients (mean age 71 yrs. 58% male) with acute dyspnea; Patients with severe renal disease or cardiogenic shock were excluded.

Intervention: Assessment including measurement of B-type natriuretic peptide or standard assessment.

Outcome: Time to discharge and total cost of treatment.

Results: Median time to discharge was significantly shorter in the intervention group when compared with the control group (8.0 vs. 11.0 days, $p=0.001$). Total cost was also significantly lower in the intervention group (\$5410 vs. \$7264, $p=0.006$). In addition, the measurement of B-type natriuretic peptide significantly reduced the need for admission to hospital and intensive care. The 30-day mortality rates were similar (10% vs. 12%, $p=0.45$).

Conclusions: In patients with acute dyspnea, measurement of B-type natriuretic peptide improves clinical outcomes (need for hospitalization or intensive care) and reduces time to discharge and total cost of treatment.



Most Commonly Used Treadmill Stress Test Protocols

- **The Bruce Protocol** – 7 stage test with each stage lasting 3 minutes. With each successive stage, the treadmill increases in both speed and gradient.
- For older individuals or those with limited exercise capacity: either The Modified Bruce or The Modified Naughton Protocol



Important Contraindications to Exercise Testing

- Acute MI, aortic dissection, pericarditis, myocarditis, pulmonary embolism
- Severe AS, arterial HTN
- Inability to exercise adequately



Most Important Prognostic Factors in Exercise Testing

- ST depression
- ST elevation
- Inadequate blood pressure compensation



Duke Treadmill Score

Weighted index combining:

1. Treadmill exercise time using standard Bruce protocol
2. Maximum net ST segment deviation (depression or elevation)
3. Exercise-induced angina

Provides diagnostic and prognostic information (such as 1-year mortality)



Patients with normal perfusion studies at peak stress have a <1%/year incidence of death or nonfatal MI and are thus often spared further invasive evaluation for assessment of their symptoms.



ACC/AHA 2002 Guidelines for Use

Stable angina, baseline ECG abnormalities, post-revascularization assessment, heart failure, patients unable to exercise, preoperative risk assessment for patients undergoing noncardiac surgery.

Contrast Echocardiography

- contrast agents injected into the bloodstream to improve imaging of the heart
- conventional agent: agitated saline (contains microbubbles of air)
- allows visualization of right heart and intracardiac shunts, most commonly patent foramen ovale (PFO) and sometimes intrapulmonary shunt
- newer contrast agents are capable of crossing the pulmonary bed and achieving left heart opacification following intravenous injection; these contrast agents improve visualization of endocardial borders and enhance evaluation of ejection fraction

Stress Testing

- exercise testing is a cardiovascular stress test using treadmill or bicycle exercise with electrocardiographic and blood pressure monitoring
- guidelines for use:
 - patients with intermediate (10-90%) pretest probability of CAD based on age, gender and symptoms
 - complete RBBB
 - ST depression <1 mm at rest
- exercise test results stratify patients into risk groups:
 - low risk patients can be treated medically without invasive testing
 - intermediate risk patients may need additional testing in the form of exercise imaging studies or cardiac catheterization
 - high risk patients should be referred for cardiac catheterization

Indications for Terminating Exercise Stress Test

- drop in systolic blood pressure of >10 mmHg from baseline despite an increase in workload, when accompanied by other evidence of ischemia
- moderate to severe angina
- ST elevation (>1 mm) in leads without diagnostic Q-waves (other than V1 or aVR)
- increasing nervous system symptoms (e.g. ataxia, dizziness, or near syncope)
- signs of poor perfusion (cyanosis or pallor)
- technical difficulties in monitoring ECG or systolic blood pressure
- patient's desire to stop
- sustained ventricular tachycardia

Interpretation

- the most commonly used ECG criteria for a positive exercise test: ≥1 mm of horizontal or downsloping ST-segment depression or elevation (at least 60 to 80 msec after the end of the QRS complex)

NUCLEAR CARDIOLOGY

- myocardial perfusion imaging (MPI) with ECG-gated single photon emission computed tomography (SPECT), using radiolabelled tracer
- role in evaluating myocardial viability, detecting ischemia, and simultaneously assessing perfusion and left ventricular function
- the degree of severity shown on the scan reveals the likelihood of further cardiac event rates independent of the patient's history, examination, resting ECG, and stress ECG result
- often denoted as MIBI scan with reference to radiolabelled tracer used
- exercise
 - treadmill test (unless contraindicated)
- vasodilator stress with intravenous drugs
 - dipyridamole (Persantine®), adenosine
 - ♦ act to increase coronary flow by vasodilation of arterioles (the resistance vessels)
- images of the heart obtained during stress and at rest 3-4h later
 - fixed defect – impaired perfusion at rest and during stress (infarcted/hibernating)
 - reversible defect – impaired perfusion only during stress (ischemic)

Tracers

- thallium-201 (²⁰¹Tl, a K analogue)
- technetium-99 (⁹⁹Tc)-labelled tracer (sestamibi/Cardiolite® or hexamibi/Myoview®)

Summary of Stress Testing

- Exercise ECG
 - initial evaluation in patients without hard-to-interpret ECGs who are able to exercise
- Exercise Stress Echo
 - when ECG is uninterpretable
 - intermediate pre-test probability with normal/equivocal exercise ECG
 - post-ACS when used to decide on potential efficacy of revascularization
 - to evaluate the clinical significance of valvular heart disease

- Dobutamine Stress Echo
 - in patients unable to exercise, with the same indications as exercise stress echo
 - to assess tissue viability
- Exercise Myocardial Perfusion Imaging (MPI)
 - when ECG is uninterpretable
 - intermediate pre-test probability with normal/equivocal exercise ECG
 - in patients with previous imaging whose symptoms have changed
 - to diagnose ischemia
- Dipyridamole/Adenosine MPI
 - to diagnose CAD in possible ACS patients with non-diagnostic ECG and negative serum biomarkers
 - when ECG is uninterpretable due to LBBB or V-paced rhythm
 - in patients unable to exercise, with the same indications as exercise MPI



Sensitivity and Specificity of Various Stress Testing

Exercise ECG (Sn 68; Sp 77)
 Stress Echocardiography (Sn 76; Sp 88)
 PET scanning (Sn 91; Sp 82)
 MIBI scanning (Sn 88; Sp 77)

Cardiac Catheterization and Angiography

- invasive: catheters are introduced percutaneously into arterial and venous circulation under conscious sedation and contrast is injected
- arterial access most commonly through the femoral artery; radial approach gaining favour especially for obese patients and outpatients dependent on driving and ambulation (occupational requirements)
- venous access through the femoral vein or internal jugular vein
- same day procedure as outpatient:
 - indications for prehospitalization: anticoagulation therapy, renal failure, diabetes, contrast allergy
- catheterization permits direct measurement of intracardiac pressures, transvalvular and mean peak pressure gradients, valve areas, cardiac output, shunt data, oxygen saturations, and visualization of coronary arteries, cardiac chambers and great vessels

Right Heart Catheterization (Swan-Ganz catheter)

- right atrial, right ventricular, pulmonary artery pressures are recorded
- Pulmonary Capillary Wedge Pressure
 - obtained by advancing the catheter to wedge into the distal pulmonary artery
 - ♦ records pressures measured from the pulmonary venous system
 - ♦ in the absence of pulmonary venous disease, will reflect left atrial pressure

Left Heart Catheterization

- systolic and end-diastolic pressure tracings recorded; left ventricular size, wall motion and ejection fraction can be assessed by injecting contrast into the left ventricle (left ventriculography)
- cardiac output (measured by the Fick oxygen method or the indicator dilution method)

Coronary Angiography

- coronary vasculature accessed via the coronary ostium
- contraindicated with severe renal failure (due to contrast agent toxicity), must check renal status

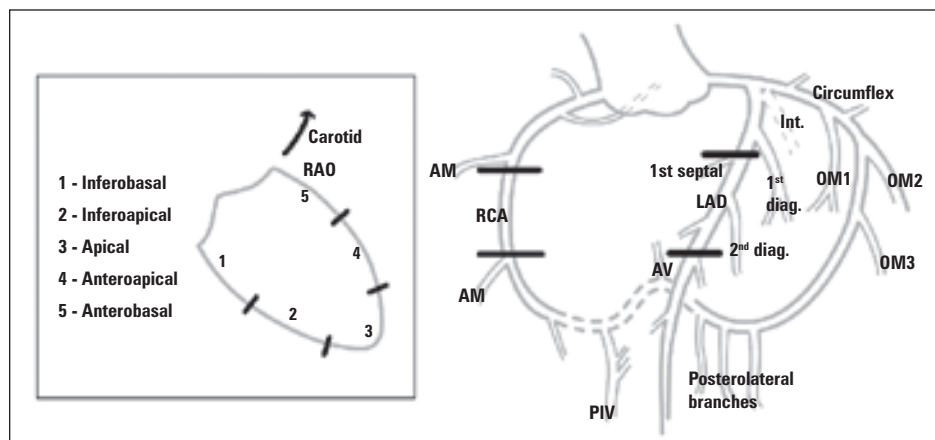


Figure 14. Coronary Angiogram Schematic (RCA = right coronary artery, AM = acute marginal, LAD = left anterior descending, OM = obtuse marginal)

Prognosticators

- angiographic variables may provide valuable information regarding lesion severity, complexity, location and prognosis



ACC/AHA 2002 Recommended Indications for Coronary Angiography

- Disabling (CCS classes III and IV) chronic stable angina despite medical therapy
- High-risk criteria on clinical assessment or non-invasive testing
- Sudden cardiac death, serious ventricular arrhythmia, or CHF
- Uncertain diagnosis or prognosis after non-invasive testing
- Inability to undergo non-invasive testing



Coronary Angiography

Gold standard for localizing and quantifying CAD.



Hemodynamically significant stenosis is defined as 70% or more narrowing of the luminal diameter.

Diagnostic Catheterization

- outcomes related to complications for diagnostic catheterization should be <1%
- procedure related complications: vascular injury, renal failure, stroke, MI
 - mortality rate 0.1-0.2%
- inadequate diagnostic procedures should occur in far fewer than 1% of cases
- provocative pharmacological agents can be used to unmask pathology
 - fluid loading may unmask latent pericardial constriction
 - afterload reduction or inotropic stimulation may be used to increase the outflow tract gradient in hypertrophic cardiomyopathy
 - coronary vasoreactive agents (e.g. methylergonovine, acetylcholine)
 - a variety of pulmonary vasoreactive agents in primary pulmonary hypertension (e.g. oxygen, calcium channel blockers, adenosine, nitric oxide, or prostacyclin)

Contrast-Enhanced CT Coronary Angiography

- fast ECG-synchronized multi-slice CT image acquisition in the heart has enabled non-invasive imaging of the coronary arterial tree
- often used to assess coronary artery and previous graft stenosis/viability that could not be seen during coronary angiography
- sensitivity = 85%, specificity = 90% for the diagnosis of obstructive coronary disease with >50% stenosis

Magnetic Resonance Imaging (MRI)

- offers high spatial resolution, eliminates the need for iodinated contrast, and does not involve exposure to ionizing radiation
- valuable in assessment of congenital cardiac anomalies, abnormalities of the aorta, and assessment of viable myocardium

CARDIAC DISEASE**Arrhythmias****Mechanisms of Arrhythmias****(I) Alterations in Impulse Formation**

This can occur due to:

A. Abnormal Automaticity

- automaticity is a property of certain cardiomyocytes to depolarize themselves to their threshold voltage so as to spontaneously generate action potentials in a rhythmical fashion
- under normal circumstances, only cells at the specialized conduction system (SAN, AVN and ventricular conduction system) exhibit natural automaticity and are thus **pacemaking** cells – the automaticity of these pacemakers can either become abnormally increased or decreased
- cells in the myocardium outside the conduction system in disease (e.g. post-MI ventricular ischemia) may inappropriately acquire the property of automaticity and contribute to abnormal depolarization. If these ectopic generators depolarize at a rate that is greater than the SAN, they assume pacemaking control and become the source of abnormal rhythm
- automaticity can be influenced by:
 - ♦ neurohormonal tone (sympathetic and parasympathetic stimulation)
 - ♦ abnormal metabolic conditions (hypoxia, acidosis, hypothermia)
 - ♦ electrolyte abnormalities
 - ♦ drugs (e.g. digitalis)
 - ♦ local ischemia/infarction
 - ♦ other cardiac pathology
- this mechanism is responsible for the accelerated idioventricular rhythm and ventricular tachycardia that often occurs 24 to 72 hours post myocardial infarction

B. Triggered Activity due to Afterdepolarizations

There are two types of triggered activity:

1. Early Afterdepolarizations

- occur in the context action potential prolongation
- consequence of the membrane potential becoming more positive during repolarization
- result in self-maintaining depolarizing oscillations of action potential, generating a tachyarrhythmia
- basis for the degeneration of QT prolongation, either congenital or acquired, into Torsades de Pointes

2. Delayed Afterdepolarizations

- occur after the action potential has fully repolarized, but before the next usual action potential, thus called a delayed afterdepolarization
- commonly occurs in situations of high intracellular calcium (digitalis intoxication, ischemia) or during enhanced catecholamine stimulation

(II) Alterations in Impulse Conduction

This can occur due to:

A. Re-Entry Circuits (see Figure 15 for detailed description)

- the presence of self-sustaining re-entry circuit causes rapid repeated depolarizations in a region of myocardium
 - ♦ e.g. myocardium that has infarcted and become ischemic will consist of non-excitable and partially excitable zones which will promote the formation of re-entry circuits

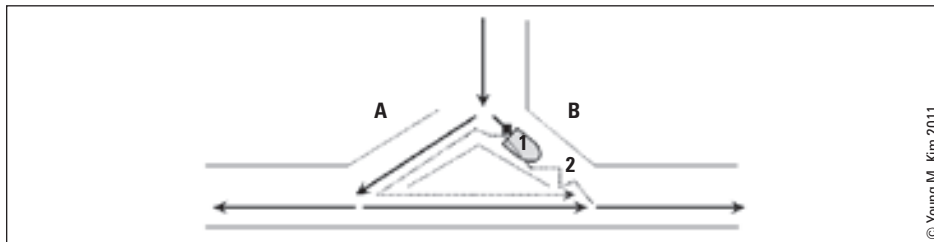


Figure 15. Mechanism of Reentry

Requires both unidirectional block (1) and slowed retrograde conduction (2). When an action potential reaches a division in the conduction path (anywhere in the myocardium), the impulse proceeds around and stimulates distal myocardium. If the action potential propagates through a block (refractory tissue) in the retrograde direction but not in the forward direction, unidirectional block is present (1). This can occur as a result of cellular dysfunction with changes in cellular refractoriness. Slowed retrograde conduction of the action potential through B (dotted line) encounters excitable tissue in A because these myocytes have had sufficient time to repolarise by this time point, and now the impulse is free to excite A again thus generating a reentry circuit.

B. Conduction Block

- ischemia, fibrosis, trauma and drugs can cause transient, permanent, unidirectional or bidirectional block
- most common cause of block is due to refractory myocardium (cardiomyocytes are in refractory period or zone of myocardium unexcitable due to fibrosis)
- if block occurs along the specialized conduction system, distal zones of the conduction system can assume pacemaking control
- conduction block can not only lead to bradycardia, but also tachycardia when impaired conduction leads to re-entry phenomenon

C. Bypass Tracts

- normally the only conducting tract from the atria to the ventricles is the AVN
- congenital development of additional, or accessory conducting tracts bypass the AVN and facilitate premature ventricular activation before normal AVN conduction
- see *Pre-Excitation Syndromes*, C19

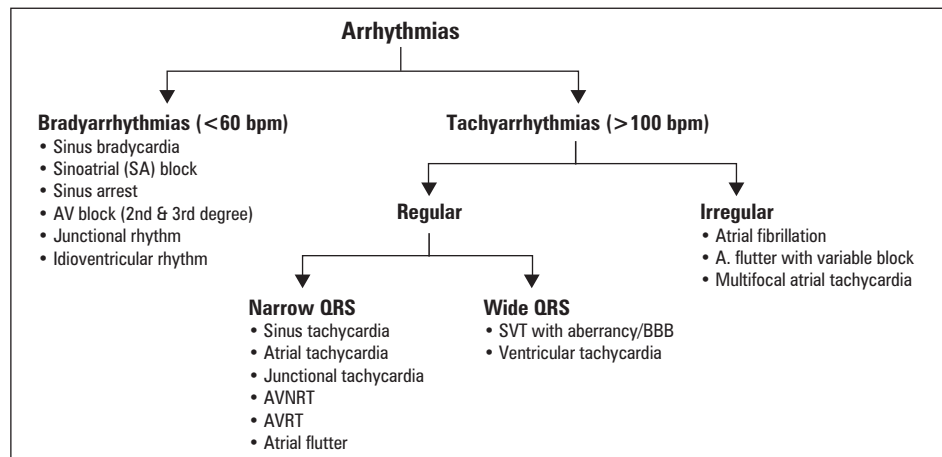


Figure 16. Clinical Approach to Arrhythmias



Bradyarrhythmias

- Examples



Sinus Arrhythmia

Normal P Waves, with variation of the P-P interval by >120 msec due to varying rate of SA node

"Respiratory SA":

- Seen more often in young adults (<31 years old)
- Normal, results from changes in autonomic tone during respiratory cycle
- Rate increases with inspiration, slows with expiration

"Non-respiratory SA":

- Seen more often in the elderly
- Can occur in the normal heart; if marked, may be due to sinus node dysfunction (e.g. in heart disease, or after digitalis toxicity)
- Usually does not require treatment

Bradyarrhythmias

SA NODAL DYSFUNCTION

Sinus Bradycardia

- P axis normal (P waves positive in I and aVF)
- rate <60 bpm
- marked sinus bradycardia (<50 bpm) may be seen in normal adults, particularly athletes, and in elderly individuals
- caused by
 - increased vagal tone or vagal stimulation
 - vomiting
 - episodes of myocardial ischemia or infarction (inferior MI)
 - sick sinus node
 - increased intracranial pressure
 - hypothyroidism
 - hypothermia
 - drugs (beta-blockers, calcium blockers, etc.)
- treatment: if symptomatic, atropine during acute episodes; pacing for sick sinus node syndrome; if drug-induced, reduction or withdrawal of drugs

Sinus Block, Pause, and Arrest

- three disorders involving the SA node; the sinus pacemaker fires but impulse fails to depolarize the atrial myocardium, resulting in no initial P wave (and consequently no QRS complex, ST segment or T wave)
- sinus block: also SA block, a complete block or failure of the sinus node to depolarize the atria; the block can last one or more cardiac cycles and is a multiple of the normal P-P interval
- sinus pause: a delay in the formation of a sinus impulse in the SA node, resulting in a temporary pause (usually >3 sec)
- sinus arrest: a longer delay in the formation of a sinus impulse in the SA node
 - there is no clear cut-off between sinus pause vs. arrest, however, if the pause lasts greater than 3x the normal P-P interval, then it may be called an arrest
 - the P-P prolongation is not phasic or gradual (unlike sinus arrhythmia) and is not a multiple of the normal P-P interval (unlike sino-atrial block)
- escape beats or rhythm may occur:
 - atrial escape: P waves with abnormal morphology
 - junctional escape: P waves not seen, or follow the QRS (retrograde P), rate 40-60 bpm
 - ventricular escape: no P wave; wide, abnormal QRS; slow rate 20-40 bpm

Sick Sinus Syndrome (SSS)

- characterized by sinus node dysfunction (marked bradycardia, sinus pause/arrest, sinoatrial block)
 - when symptomatic, electronic pacemaker is indicated
- frequently associated with episodes of atrial tachyarrhythmias ("tachy-brady syndrome")
- usually require a combination of a pacemaker for bradycardia and medications (beta-blocker, calcium channel blocker, and/or digoxin, initiated after pacemaker insertion) for tachycardia

AV Conduction Blocks

1st Degree AV Block

- prolonged PR interval (>200 msec)
- frequently found among otherwise healthy adults
- no treatment required

2nd Degree AV Block

- some of the atrial impulses are not conducted to the ventricles
- can describe block by ratio of P waves to # of QRS (e.g. 2:1, 3:1, 4:1 increases in severity)
- second degree AV block is further subdivided into:
 - Type I (Mobitz I) 2nd Degree AV Block
 - ♦ a gradual prolongation of the PR interval precedes the failure of conduction of a P wave (Wenckebach phenomenon)
 - ♦ AV block is usually in AV node (proximal)
 - triggers (usually reversible): increased vagal tone (eg. following surgery), RCA-mediated ischemia
 - not an indication for temporary or permanent pacing



Figure 17. Second Degree AV Block with Wenckebach Phenomenon (Mobitz I) (4:3 conduction) (Lead V₁)

- Type II (Mobitz II) 2nd Degree AV Block
 - ♦ the PR interval is constant; there is an abrupt failure of conduction of a P wave
 - ♦ AV block is usually distal to the AV node (ie. His bundle)
 - ♦ increased risk of high grade or 3rd degree AV block

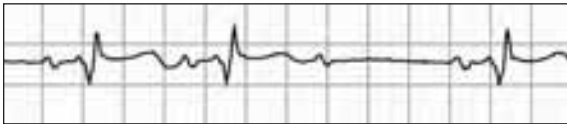


Figure 18. Second Degree AV Block (Mobitz II) (3:2 conduction) (Lead V₁)



Type II (Mobitz II)
2° Type II AV block is an indication for permanent pacing.

2:1 AV Block

- often not possible to determine whether the block is type I or type II
- prolonged or repeated recordings may clarify the diagnosis

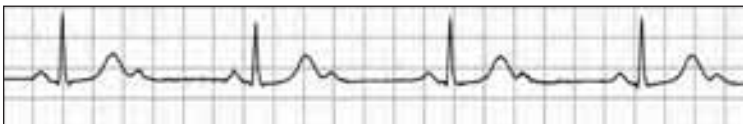


Figure 19. 2:1 AV Block (Lead II)

3rd Degree AV Block

- complete failure of conduction of the supraventricular impulses to the ventricles
- ventricular depolarization initiated by an escape pacemaker distal to the block
- QRS can be narrow or wide (junctional vs. ventricular escape rhythm)
- PP and RR intervals are constant, variable PR intervals
- no relationship between P waves and QRS complexes (P waves “marching through”)
- management (see *Electrical Pacing*, C21)



Figure 20. Third Degree AV Block (Complete Heart Block) (Lead II)



Tachyarrhythmias

- Examples

Supraventricular Tachyarrhythmias

Presentation for SVT (and pre-excitation syndromes)

- symptoms can include: palpitations, dizziness, dyspnea, chest discomfort, presyncope/syncope
- may precipitate congestive heart failure (CHF), hypotension, or ischemia in patients with underlying disease
- untreated tachycardias can cause cardiomyopathy (rare, potentially reversible with treatment of SVT's)
- includes supraventricular and ventricular rhythms

Supraventricular Tachyarrhythmias (SVT)

- tachyarrhythmias that originate in the atria or AV junction
- this term is used when a more specific diagnosis of mechanism and site of origin cannot be made
- characterized by narrow QRS, unless there is pre-existing BBB or aberrant ventricular conduction (abnormal conduction due to a change in cycle length)

Sinus Tachycardia

- sinus rhythm with rate >100 bpm
- occurs in normal subjects with increased sympathetic tone (exercise, emotions, pain), alcohol use, caffeinated beverages, drugs (e.g. beta-adrenergic agonists, anticholinergic drugs, etc.)
- etiology: fever, hypotension, hypovolemia, anemia, thyrotoxicosis, heart failure, MI, shock, pulmonary embolism, etc.
- treatment: treat underlying disease; consider beta-blocker if symptomatic, CCB if beta-blockers contraindicated

Premature Beats

- premature atrial contraction (PAC, Figure 25)
 - ectopic supraventricular beat originating in the atria
 - P wave morphology of the PAC usually differs from that of a normal sinus beat
- junctional premature beat
 - ectopic supraventricular beat that originates in the vicinity of the AV node
 - P wave is usually not seen or an inverted P wave is seen and may be before or closely follow the QRS complex
 - treatment usually not required

Atrial Flutter

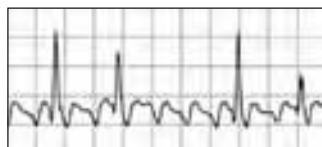


Figure 21. Atrial Flutter with Variable Block

- rapid, regular atrial depolarization from a macro re-entry circuit within the atrium (most commonly the right atrium)
- atrial rate 250-350 bpm, usually 300 bpm
- AV block usually occurs; it may be fixed (2:1, 3:1, 4:1, etc.) or variable
- etiology: CAD, thyrotoxicosis, MV disease, cardiac surgery, COPD, pulmonary embolism, pericarditis
- ECG: sawtooth flutter waves (most common type of flutter) in inferior leads (II, III, aVF); narrow QRS (unless aberrancy)
- in atrial flutter with 2:1 block, carotid sinus massage (first check for bruits), Valsalva maneuver or adenosine may decrease AV conduction and bring out flutter waves
- treatment
 - acute: if unstable (e.g. hypotension, CHF, angina): electrical cardioversion
 - if stable
 - (1) rate control: beta-blocker, diltiazem, verapamil, or digoxin
 - (2) chemical cardioversion: sotalol, amiodarone, type I antiarrhythmics or electrical cardioversion
 - anticoagulation guidelines same as for patients with AF (see *Atrial Fibrillation*, C17)
 - long-term: antiarrhythmics, catheter radiofrequency (RF) ablation (success rate dependent on site of origin of atrial flutter)

Multifocal Atrial Tachycardia (MAT)

- irregular rhythm caused by presence of 3 or more atrial foci (may mimic AF)
- atrial rate 100-200 bpm; at least 3 distinct P wave morphologies and PR intervals vary, some P waves may not be conducted
- occurs more commonly in patients with COPD, and hypoxemia; less commonly in patients with hypokalemia, hypomagnesemia, sepsis, theophylline or digitalis toxicity
- treatment: treat the underlying cause; CCBs may be used (e.g. diltiazem, verapamil), beta-blockers may be contraindicated because of severe pulmonary disease
- no role for electrical cardioversion, antiarrhythmics or ablation

Atrial Fibrillation (AF)

- most common sustained arrhythmia
- incidence increases with age (10% of population >80 years old)
- symptoms: palpitations, fatigue, syncope and may precipitate or worsen heart failure
- may be associated with thromboembolic events (4%/year in nonvalvular AF)
- **initiation**
 - single circuit re-entry and/or ectopic foci act as aberrant generators producing atrial tachycardia (350-600)
 - impulses then conduct irregularly across the atrial myocardium to give rise to fibrillation
 - in some cases, ectopic foci have also been mapped to the pulmonary vein ostia and can be ablated
- **maintenance**
 - the tachycardia causes atrial structural and electrophysiological remodelling changes that further promote AF; thus the longer the patient is in AF, the more difficult it is to convert back to sinus rhythm
- **consequences**
 - the AV node irregularly filters incoming atrial impulses producing an irregular ventricular response of <200 bpm and the tachycardia leads to suboptimal cardiac output
 - fibrillatory conduction of the atria promotes blood stasis increasing the risk of thrombus formation – AF is an important risk factor for stroke

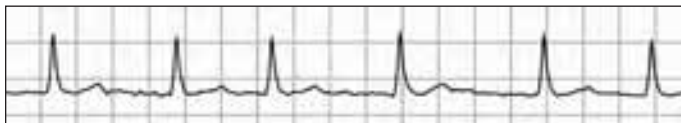
Table 3. CHADS2 Risk Prediction for Non-Valvular AF

Risk Factor	Points	CHADS2 Score	Stroke Risk (%/Yr)	Anticoagulation Recommendation
Congestive Heart Failure	1	0-1	1.9-2.8 (low)	aspirin 81-325 mg daily
Hypertension	1	2-3	4.0-5.9 (mod)	coumadin (INR 2-3)
Age >75	1	4-6	8.5-18.2 (high)	coumadin (INR 2-3)
Diabetes	1			
Stroke/TIA (prior)	2			

JAMA 2001; 285(22):2864-70

AF on ECG

- no organized P waves due to rapid atrial activity (350-600 bpm) causing a chaotic fibrillatory baseline
- irregularly irregular ventricular response (typically 100-180bpm), narrow QRS (unless aberrancy or previous BBB)
- wide QRS complexes due to aberrancy may occur following a long-short cycle sequence (“Ashman phenomenon”)
- loss of atrial contraction, thus no “a” wave seen in JVP, no S4 on auscultation

**Figure 22. Atrial Fibrillation (Lead II)****Management (adapted from ACC/AHA/ESC guidelines 2006)****Major objectives (RACE)**

1. Rate control: beta-blockers, diltiazem, verapamil (in patients with heart failure: digoxin, amiodarone)
2. Anti-coagulation: prevent thromboembolism
 - assess stroke risk: determine CHADS2 score in patients with nonvalvular AF
 - if no risk factors, ASA 81-325 mg daily
 - 1 moderate risk factor, ASA or warfarin (INR 2.0-3.0, target 2.5)
 - ≥2 moderate risk factors or any high risk factor (prior stroke, TIA or embolism, mitral stenosis, prosthetic valve), warfarin
3. Cardioversion (electrical)
 - if AF <24-48 hrs, can usually cardiovert without anticoagulation
 - if AF >24-48 hrs, anticoagulate for 3 weeks prior and 4 weeks after cardioversion
 - if patient unstable (hypotensive, active angina due to tachycardia, uncontrolled heart failure), should cardiovert immediately
4. Etiology
 - HTN, CAD, valvular disease, pericarditis, cardiomyopathy, myocarditis, ASD, following surgery, PE, COPD, thyrotoxicosis, SSS (Sick Sinus Syndrome), alcohol (“holiday heart”)
 - may present in young patients without demonstrable disease (“lone AF”) and in the elderly without underlying heart disease
 - restore normal sinus rhythm if feasible

Atrial Fibrillation – AFFIRM Trial

NEJM 2002; 347:1825-33

Study: Randomized, multicenter trial with mean follow-up of 3.5 years.**Population:** 4060 patients (mean age 70 yrs, 61% male, 89% white) with atrial fibrillation and a high risk of stroke or death.**Intervention:** Rate control (β-blockers, calcium channel blockers, or digoxin alone or in combination) vs. rhythm control (antiarrhythmic drug chosen by the treating physician).**Primary Outcome:** All cause mortality.**Results:** There was no difference in mortality – or composite mortality, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest – between the two groups. There were more incidents of hospitalizations (80.1% vs. 73%, $p < 0.001$) and adverse events (Torsades de pointes (12 vs. 2, $p = 0.007$), pulseless or bradycardic arrest (9 vs. 1, $P = 0.01$), pulmonary event (108 vs. 24, $p < 0.001$) gastrointestinal event (127 vs. 35, $p < 0.001$), prolonged QT interval (31 vs. 4, $p \leq 0.001$), bradycardia (105 vs. 64, $p = 0.001$) in the rhythm-control group. Decreased risk of death in the rate control arm in sub-groups.**Conclusion:** Rate-control was as effective as rhythm-control in atrial fibrillation and is better tolerated. There were more hospitalizations, incidents in the rhythm-control group.

Oral Anticoagulants versus Antiplatelet Therapy for Preventing Stroke in Patients with Non-Valvular Atrial Fibrillation and No History of Stroke or Transient Ischemic Attacks

Cochrane Database Syst Rev 2007; (3):CD006186
Study: Cochrane Systematic Review. 8 RCTs with mean 1.9 years of follow-up.

Population: 9598 total patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attack.

Intervention: Long-term adjusted-dose warfarin versus aspirin

Outcome: All cause mortality, all stroke, vascular death, myocardial infarctions.

Results: Dose-adjusted warfarin therapy significantly reduced all stroke (OR 0.68, 95%CI 0.54 – 0.85), ischemic stroke (OR 0.53, 95%CI 0.41 – 0.68), and systemic emboli risk (OR 0.48, 95%CI 0.25 – 0.90). There was no significant difference in disabling or fatal strokes, MI, vascular death, or all cause mortality. There was a significantly increased risk of intracranial hemorrhage with warfarin therapy versus aspirin (OR 1.98, 95%CI 1.20 – 3.28).

Conclusion: Long-term adjusted-dose warfarin significantly reduces all stroke and embolic risks but does not reduce risk of disability or mortality and carries a significant intracranial hemorrhage risk. The threshold of benefit for anti-coagulation versus anti-platelet therapy remains controversial.

Additional Management Points Regarding Atrial Fibrillation

- recent studies of patients with atrial fibrillation suggest that there is no difference in long-term survival when treating patients with a rhythm-control versus rate-control strategy
- however, many patients with a significant underlying structural heart lesion (e.g. acute MI, history of congestive heart failure), valvular lesions (mitral stenosis, mitral regurgitation, aortic stenosis), hypertrophic cardiomyopathy, cardiac amyloid, other cardiomyopathies, pericardial disease, congenital heart lesions) will not tolerate atrial fibrillation well (since many dependent on atrial kick) and these patients should be cardioverted (chemical or electrical) as soon as possible

Newly Discovered AF

- anticoagulants may be beneficial if high risk for stroke
- if the episode is self limited and not associated with severe symptoms, no need for antiarrhythmic drugs
- if AF persists, 2 options:
 - rate control and anticoagulation (as indicated above)
 - cardioversion (as above)

Recurrent AF/Permanent AF

- if episodes are brief or minimally symptomatic, antiarrhythmic drug may be avoided; rate control and anticoagulation are appropriate
- patients who have undergone at least one attempt to restore sinus rhythm may remain in AF after recurrence: permanent AF may be accepted (with rate control and antithrombotics as indicated by CHADS2 score) in certain clinical situations
- if symptoms are bothersome or episodes are prolonged, antiarrhythmic drugs should be used
 - no or minimal heart disease: flecainide, propafenone or sotalol
 - LV dysfunction: amiodarone
 - CAD: beta-blockers, amiodarone

AV Nodal Re-Entrant Tachycardia (AVNRT)

- re-entrant circuit using the dual pathways (fast conducting beta fibres and slow conducting alpha fibres) within or near the AV node; often found in the absence of structural heart disease; cause is commonly idiopathic, although familial AVNRT has been reported
- sudden onset and offset
- fast regular rhythm; rate 150-250 bpm
- usually initiated by a supraventricular or ventricular premature beat
- AVNRT accounts for 60-70% of all paroxysmal SVTs
- retrograde P waves may be seen but are usually lost in the QRS complex
- treatment
 - acute: Valsalva or carotid massage, adenosine is first choice if unresponsive to vagal maneuvers; if no response, try metoprolol, digoxin, diltiazem; electrical cardioversion if patient hemodynamically unstable (hypotension, angina or CHF)
 - long-term: 1st line: beta-blocker, diltiazem, digoxin, 2nd: anti-arrhythmic drugs (flecainide, propafenone), 3rd: catheter ablation



The carotid massage is actually a constant pressure directed posteriorly against the carotid artery for 5-10 seconds. Always listen for bruits before palpation.

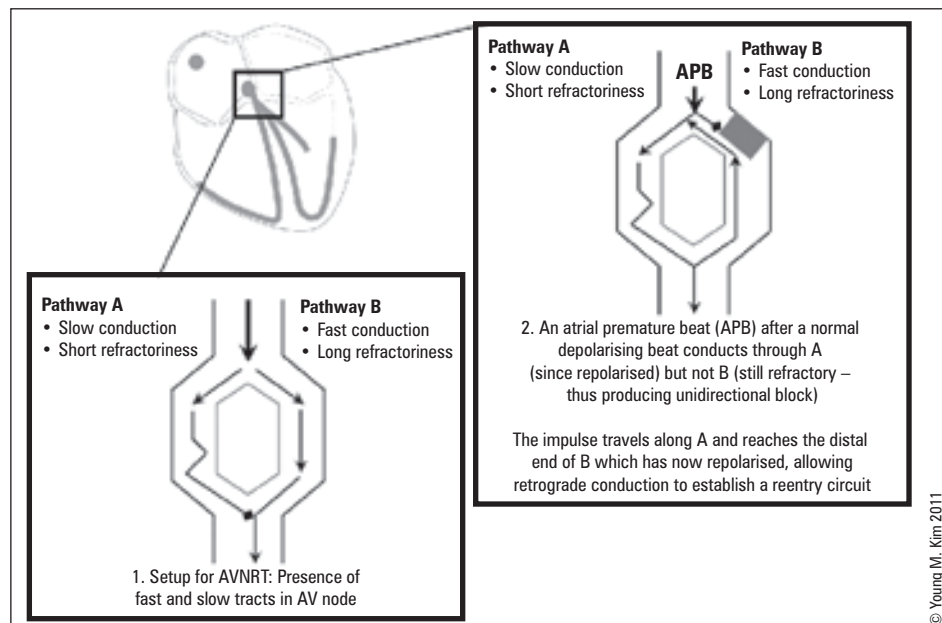


Figure 23. Mechanism for AV Nodal Re-Entry

Pre-Excitation Syndromes

- refer to a subset of supraventricular tachyarrhythmias, mediated by an accessory pathway, which can lead to ventricular pre-excitation

Wolff-Parkinson-White (WPW) Syndrome

- congenital defect present in 1.5-2/1000 of the general population
- an accessory conduction tract (Bundle of Kent; can be in right or left atrium) abnormally allows early electrical activation of part of one ventricle
- impulses travel at a greater conduction velocity across the Bundle of Kent thereby effectively 'bypassing' AV node
- since the ventricles are activated earlier, the ECG shows early ventricular depolarization in the form of initial slurring of the QRS complex – the so called delta wave
- atrial impulses that conduct to the ventricles through both the Bundle of Kent and the normal AV node/His-Purkinje system generate a broad "fusion complex"
- ECG features of WPW
 - PR interval <120 msec
 - "delta wave": slurred upstroke of the QRS (the leads with the delta wave vary with site of bypass)
 - widening of the QRS complex due to the premature activation
 - secondary ST segment and T wave changes
 - tachyarrhythmias may occur, most often AVRT and AF

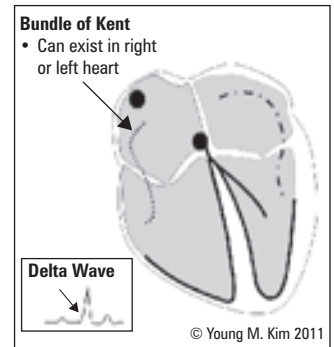


Figure 24. Accessory pathway conduction in WPW causes early ventricular activation leading to the appearance of a delta wave (slurred upstroke of the QRS) on the ECG before usual conduction occurs across the AVN

AF in WPW Patients

- AF is the index arrhythmia in up to 20 percent of patients with WPW syndrome
 - it is usually intermittent rather than persistent or permanent
- rapid atrial depolarizations in AF are conducted through the bypass tract which is not able to filter impulses like the AVN
- consequently, the ventricular rate becomes extremely rapid (>200 bpm) and the QRS complex widens
- treatment: electrical cardioversion, IV procainamide or IV amiodarone
 - do not use drugs that slow AV node conduction (digoxin, beta blockers) as this may cause preferential conduction through the bypass tract and then precipitate VF
 - long-term: ablation of bypass tract when possible

AV Re-Entrant Tachycardia (AVRT)

- re-entrant loop via accessory pathway and normal conduction system
- initiated by a premature atrial or ventricular complex
- orthodromic AVRT: stimulus from a premature complex travels up the bypass tract (V to A) and down the AV node (A to V) with narrow QRS complex (no delta wave because stimulus travels through normal conduction system)
 - comprises 95 percent of the reentrant tachycardias associated with WPW syndrome
- antidromic AVRT: more rarely the stimulus goes up the AV node (V to A) and down the bypass tract (A to V); wide and abnormal QRS as ventricular activation is only via the bypass tract
- treatment
 - acute: similar to AVNRT except avoid long-acting AV nodal blockers, e.g. digoxin and verapamil
 - long-term: for recurrent arrhythmias, ablation of the bypass tract is recommended
 - ♦ drugs such as flecainide and procainamide can be used

Ventricular Tachyarrhythmias

Premature Ventricular Contraction (PVC) or Ventricular Premature Beat (VPB)

- QRS width >120 msec, no preceding P wave, bizarre QRS morphology
- origin: LBBB pattern = RV site; RBBB pattern = LV site
- PVCs may be benign but are usually significant in the following situations:
 - consecutive ($\geq 3 = VT$) or multifocal (varied origin)
 - PVC falling on the T wave of the previous beat ("R on T phenomenon"): may precipitate ventricular tachycardia or VF

Accelerated Idioventricular Rhythm

- ectopic ventricular rhythm with rate 50-100 bpm
- more frequently occurs in the presence of sinus bradycardia, and is easily overdriven by a faster supraventricular rhythm
- frequently occurs in patients with acute myocardial infarction or other types of heart disease (cardiomyopathy, hypertensive, valvular) but it does not affect prognosis and does not usually require treatment

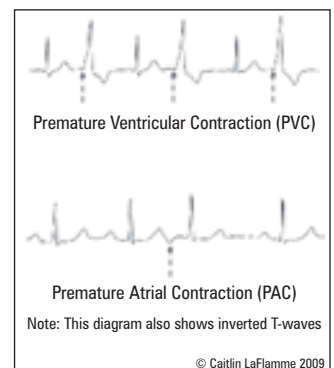


Figure 25. PVC (with bigeminy pattern) and PAC


Arrhythmias that May Present as a Wide QRS Tachycardia

- Ventricular tachycardia
- SVT with aberrant conduction (rate related)
- SVT with preexisting BBB or nonspecific intraventricular conduction defect
- AV conduction through a bypass tract in WPW patients during an atrial tachyarrhythmia (e.g. atrial flutter, atrial tachycardia)
- Antidromic AVRT in WPW patients (see *Pre-excitation Syndromes*, C19)

Ventricular Tachycardia (VT)

- 3 or more consecutive ectopic ventricular complexes (Figure 26)
 - rate >100 bpm (usually 140-200)
 - ventricular flutter: if rate >200 bpm and complexes resemble a sinusoidal pattern
 - “sustained VT” if it lasts longer than 30 sec
 - ECG characteristics: wide regular QRS tachycardia (QRS usually >140 msec); AV dissociation; bizarre QRS pattern. Also favour Dx of VT: left axis or right axis deviation, nonspecific intraventricular block pattern, monophasic or biphasic QRS in V1 with RBBB, QRS concordance in V1-V6
 - occasionally during VT supraventricular impulses may be conducted to the ventricles generating QRS complexes with normal or aberrant supraventricular morphology (“ventricular capture”) or summation pattern (“fusion complexes”)
- **monomorphic VT**
 - identical complexes with uniform morphology
 - more common than polymorphic VT
 - typically result from intraventricular re-entry circuit
 - potential causes: chronic infarct scarring, acute MI/ischemia, cardiomyopathies, myocarditis, arrhythmogenic right ventricular dysplasia, idiopathic, drugs (e.g. cocaine), electrolyte disturbances
- **polymorphic VT**
 - complexes with constantly changing morphology, amplitude, and polarity
 - more frequently associated with hemodynamic instability due to faster rates (typically 200-250 bpm) vs. monomorphic VT
 - potential causes: acute myocardial infarction, severe or silent ischemia, and predisposing factors for QT prolongation (see below in Torsades de Pointes)
- treatment
 - sustained VT (longer than 30 seconds) is an emergency, requiring immediate treatment
 - hemodynamic compromise – electrical cardioversion
 - no hemodynamic compromise – electrical cardioversion, lidocaine, amiodarone, type Ia agents (procainamide, quinidine)

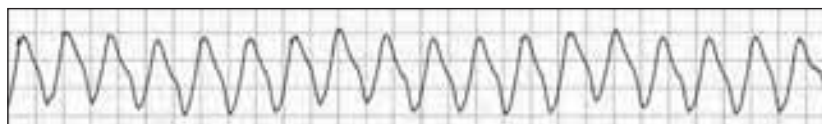


Figure 26. Ventricular Tachycardia (Monomorphic)

Table 4. Wide Complex Tachycardia: Clues for Differentiating VT vs. SVT with Aberrancy*

Clinical Clues		ECG Clues	
Presenting symptoms	Not helpful	AV dissociation	VT
History of CAD and previous MI	VT	Capture or fusion	VT
Physical Exam		QRS width >140 msec	VT
Cannon “a” waves	VT	Extreme axis deviation	VT
Variable S1	VT	(left or right superior axis)	
Carotid sinus massage/adenosine terminates arrhythmia	SVT**	Positive QRS concordance (R wave across chest leads)	VT
		Negative QRS concordance (S wave across chest leads)	May suggest VT
		Axis shift during arrhythmia	VT (polymorphic)

*If patient >65 and previous MI or structural heart disease, then chance of VT >95%

**May terminate VT in some patients with no structural heart disease

Torsades de Pointes

- a variant of polymorphic VT that occurs in patients with baseline QT prolongation – “twisting of the points” (Figure 27)
- looks like usual VT except that QRS complexes “rotate around the baseline” changing their axis and amplitude
- ventricular rate greater than 100 bpm, usually 150-300 bpm
- etiology: patients with prolonged QT intervals are predisposed
 - congenital long QT syndromes
 - drugs – e.g. Class IA (quinidine), Class III (sotalol), phenothiazines (TCAs), erythromycin, quinolones, antihistamines
 - electrolyte disturbances – hypokalemia, hypomagnesemia
 - nutritional deficiencies causing above electrolyte abnormalities
- treatment: IV magnesium, temporary pacing, isoproterenol and correct underlying cause of prolonged QT, electrical cardioversion if hemodynamic compromise

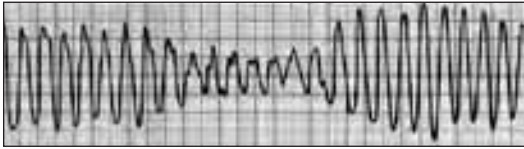


Figure 27. Torsades de Pointes

Ventricular Fibrillation (VFib)

- chaotic ventricular arrhythmia, with very rapid irregular ventricular fibrillatory waves of varying morphology (Figure 28)
- terminal event, unless advanced cardiac life-support (ACLS) procedures are promptly initiated to maintain ventilation and cardiac output, and electrical defibrillation is carried out
- most frequent cause of sudden death
- refer to ACLS algorithm for complete therapeutic guidelines

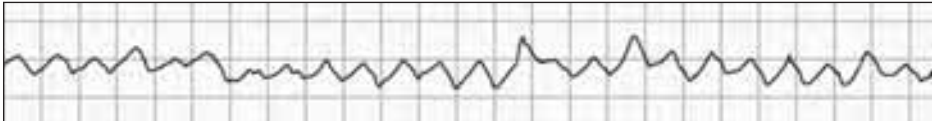


Figure 28. Ventricular Fibrillation

Electrophysiology (EPS) Studies

- invasive test for the investigation and treatment of cardiac rhythm disorders using intracardiac catheters
- provide detailed analysis of the arrhythmia mechanism and precise site of origin when ECG data are nondiagnostic or unobtainable
- bradyarrhythmias: define the mechanisms of sinus node dysfunction and localize site of AV conduction block
- tachyarrhythmias: map for possible ablation or to assess inducibility of ventricular tachycardia

Electrical Pacing

- the decision to implant a pacemaker usually is based on symptoms of a bradyarrhythmia or tachyarrhythmia in the setting of heart disease

Pacemaker Indications

- SA node dysfunction (most common): symptomatic bradycardia \pm hemodynamic instability
 - common manifestations include: syncope, near syncope, transient lightheadedness, or severe fatigue
- SA node dysfunction is commonly caused by: intrinsic disease within the sinus node (e.g. idiopathic degeneration, fibrosis, ischemia, or surgical trauma), abnormalities in autonomic nervous system function, and drug effects
- AV nodal-infranodal block: Mobitz II, complete heart block

Pacing Techniques

- temporary: transvenous (jugular, subclavian, femoral) or external pacing
- permanent: transvenous into RA, apex of RV or both
 - can sense and pace atrium, ventricle or both
 - new generation: rate responsive, able to respond to physiologic demand
 - biventricular

Table 5. Pacemaker Nomenclature

Position I	Position II	Position III	Position IV	Position V
Chamber paced	Chamber sensed	Response to sensing	Programmability	Tachyarrhythmia control
O = None	O = None	O = None	O = None	O = None
A = Atrium	A = Atrium	I = Inhibited	R = Rate modulation	P = Pace
V = Ventricle	V = Ventricle	T = Triggered		S = Shock
D = Dual (A+V)	D = Dual (A+V)	D = Dual (I + T)		D = Dual (P+S)

- examples of commonly used pacemakers
 - VVI: single lead in ventricle, pacemaker inhibited in response to a sensed beat in ventricle; protect patient from bradycardia
 - DDD: separate leads in atrium and ventricle; pace atrium if atrium does not contract; once an atrial event has occurred (whether paced or native) device will ensure that ventricular contraction follows; device is inhibited in the presence of sinus rhythm and normal AV conduction, provides physiologic pacing

Systematic Review: Implantable Cardioverter Defibrillators for Adults with Left Ventricular Systolic Dysfunction

Ann Intern Med 2007; 147:251-62

Study: Meta-review of 12 RCTs used for Implantable Cardioverter Defibrillator (ICD) efficacy, 5 RCTs and 48 observational studies for effectiveness, and 21 RCTs and 43 observational studies for safety review.

Population: 8516 patients for ICD efficacy, 26 840 patients for effectiveness, and 86 809 patients for safety review with left ventricular ejection fraction ≤ 0.35 .

Intervention: Implantable Cardioverter Defibrillator implantation.

Outcomes: All-cause mortality and adverse events

Results: ICDs reduced all-cause mortality by 20% (95% CI, 10% - 29%; $I^2 = 44.4\%$) with greatest reduction (54%) in sudden cardiac death (CI, 37% - 63%; $I^2 = 0\%$). Observational studies had a reduced relative risk of 0.54 for all-cause mortality versus RCTs (CI 0.43 - 0.58, $I^2 = 60.4\%$). Rates of success of ICD implantation were 99% (CI 98.8% - 99.3%) with a 1.2% (CI 0.9% - 1.5%) chance of peri-implantation death. Post-implantation complications (per 100 patient-years) were: 1.4 (CI 1.2 - 1.6) device malfunctions; 1.5 (CI 1.3 - 1.8) lead problems; 0.6 (CI 0.5 - 0.8) implant site infection; and 19.1 (CI 16.5 - 22.0) inappropriate discharges in RCTs versus a rate of 4.9 (CI 4.5 - 5.3) inappropriate discharges in observational studies.

Conclusion: ICDs are safe and effective in reducing mortality in adult patients with LV systolic dysfunction, but carry significant risks of inappropriate discharges. Differences between RCTs and observational studies show that improved risk stratification of patients may further improve outcomes and reduce adverse events.

Implantable Cardioverter Defibrillators (ICDs)

- sudden cardiac death (SCD) usually results from ventricular fibrillation (VFib), sometimes preceded by monomorphic or polymorphic ventricular tachycardia (VT)
- ICDs detect ventricular tachyarrhythmias and are highly effective in terminating VT/VFib and in aborting SCD
- several studies demonstrate mortality benefit vs. antiarrhythmics in 2° prevention (AVID, CASH, CIDS)
- benefit for 1° prevention of SCD in patients with ischemic and non-ischemic cardiomyopathy, depressed left ventricular ejection fraction (LVEF), prolonged QRS
- see *Heart Failure*, C32 for current treatment recommendations

Catheter Ablation

Techniques

- radiofrequency (RF) energy: a low-voltage high-frequency form of electrical energy (similar to cautery). RF energy produces small, homogeneous, necrotic lesions approximately 5-7 mm in diameter and 3-5 mm in depth

Indications

- paroxysmal SVT
 - AVNRT: accounts for more than half of all cases
- accessory pathway (orthodromic reciprocating tachycardia): 30% of SVT
 - re-entrant rhythm, with an accessory AV connection as the retrograde limb
 - corrected by targeting the accessory pathway
- atrial flutter: flutter focus in RA
- atrial fibrillation: potential role for pulmonary vein ablation
- ventricular tachycardia: commonly arises from the right ventricular outflow tract and less commonly originates in the inferoseptal left ventricle near the apex (note: majority of cases of VT are due to scarring from previous MI and cannot be ablated)

Major Complications

- approximately 1% of patients
- death: 0.1-0.2%
- cardiac: high grade AV block requiring permanent pacemaker, tamponade, pericarditis
- vascular: hematoma, vascular injury, thromboembolism, TIA/stroke
- pulmonary: pulmonary embolism

Ischemic Heart Disease (IHD)

Epidemiology

- most common cause of cardiovascular morbidity and mortality
- atherosclerosis and thrombosis are the most important pathogenetic mechanisms
- male:female ratio = 2:1 with all age groups included (Framingham study), 8:1 for age <40 , 1:1 for age >70
- peak incidence of symptomatic IHD is age 50-60 (men) and 60-70 (women)
- for primary prevention of ischemic heart disease, please see [Family Medicine](#), FM17

Table 6. Risk Factors for Atherosclerotic Heart Disease

Major Risk Factors	Minor Risk Factors
Smoking	Male, postmenopausal female
Diabetes mellitus (DM)	Obesity
Hypertension (HTN)	Sedentary lifestyle
Family history (FHx) of MI	Hyperhomocysteinemia
First degree male relative <55	
First degree female relative <65	
Hyperlipidemia	

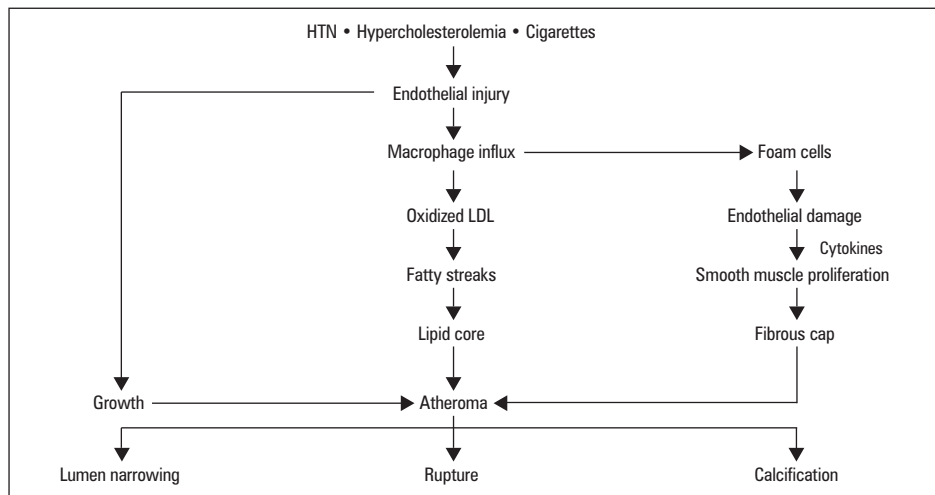


Figure 29. Pathophysiology of Atherosclerosis

Chronic Stable Angina

Definition

- symptom complex resulting from an imbalance between oxygen supply and demand in the myocardium
- factors influencing supply
 - luminal diameter (most important factor)
 - duration of diastole (important for coronary artery perfusion)
 - hemoglobin
 - SaO₂
- factors influencing demand
 - heart rate
 - contractility
 - wall stress

Etiology and Pathophysiology

- decreased myocardial oxygen supply
 - atherosclerosis, vasospasm
 - tachycardia (decreased duration of diastolic coronary perfusion)
 - anemia
 - hypoxemia
 - congenital anomalies
- increased myocardial oxygen demand
 - tachycardia
 - hyperthyroidism (increased contractility, increased HR)
 - myocardial hypertrophy, aortic stenosis

Signs and Symptoms

- typical: retrosternal chest pain, tightness or discomfort radiating to left (± right) shoulder/arm/neck/jaw, associated with diaphoresis, nausea, anxiety
- predictably precipitated by the “3 E’s”: Exertion, Emotion and Eating
- brief duration, lasting <10-15 minutes and typically relieved by rest and nitrates
- Levine’s sign: clutching fist over sternum when describing chest pain
- anginal equivalents: dyspnea, acute left ventricular failure, flash pulmonary edema

Clinical Assessment

- history, physical and directed risk factor assessment
- labs: Hb, fasting glucose, fasting lipid profile
- ECG (at rest and during episode of chest pain if possible)
- CXR (suspected heart failure, valvular disease, pericardial disease, aortic dissection/aneurysm, or signs or symptoms of pulmonary disease)
- stress testing (see *Cardiac Diagnostic Tests*, C5) or angiography
- echocardiography
 - to assess systolic murmur suggestive of aortic stenosis (AS), mitral regurgitation (MR) and/or hypertrophic cardiomyopathy (HCM)
 - to assess LV function in patients with Hx of prior MI, pathological Q waves, signs or symptoms of congestive heart failure (CHF)



Chronic stable angina is most often due to a fixed stenosis caused by an atheroma.

Acute coronary syndromes are the result of plaque rupture.



Canadian Cardiovascular Society (CCS) Functional Classification of Angina

- **Class I:** ordinary physical activity (walking, climbing stairs) does not cause angina; angina with strenuous, rapid, or prolonged activity.
- **Class II:** slight limitation of ordinary activity: angina brought on at >2 blocks on level or climbing >1 flight of stairs or by emotional stress.
- **Class III:** marked limitation of ordinary activity: angina brought on at <2 blocks on level or climbing <1 flight of stairs.
- **Class IV:** inability to carry out any physical activity without discomfort; angina may be present at rest.

Differential Diagnosis

- cardiovascular
 - aortic dissection
 - pericarditis
 - myocardial infarction (MI)
- respiratory (e.g. PE, pneumothorax, pneumonia)
- gastrointestinal (e.g. peptic ulcer disease, gastroesophageal reflux disease, esophagitis, gastritis, esophageal spasm, esophageal rupture)
- musculoskeletal (e.g. rib fracture, costochondritis, muscle spasm)
- neurological (e.g. herpes zoster)
- psychiatric (e.g. anxiety)

Optimal Medical Therapy with or without PCI for Stable Coronary Disease. COURAGE Trial
NEJM 2007; 356:1503-16

Study: Randomized, controlled trial with median follow-up of 4.6 years.

Population: 2287 patients who had objective evidence of myocardial ischemia and significant stable coronary artery disease.

Intervention: Patients were randomized to receive intensive pharmacologic therapy and lifestyle intervention with or without percutaneous coronary intervention (PCI).

Outcome: Primary outcome was all-cause mortality and nonfatal myocardial infarction (MI). Secondary outcome had additional events of stroke, all MI, and hospitalization for unstable angina with negative biomarkers.

Results: There was no significant difference in primary (unadjusted hazard ratio: 1.05; $P=0.62$) or secondary outcomes (hazard ratio: 1.05; $P=0.62$) between the PCI and non-PCI intervention groups. The PCI group had significantly lower rates of revascularization at 4.6 years of follow-up (hazard ratio 0.60, $P<0.001$) and was more angina-free in the first 4 years of follow-up.

Conclusions: PCI as an adjunct in initial management in patients with significant stable coronary artery disease does not reduce mortality, MI, stroke or hospitalization for ACS, but does provide angina relief and reduced risk of revascularization.

Treatment of Chronic Stable Angina**1. General measures**

- goals: to reduce myocardial oxygen demand and/or increase oxygen supply
- lifestyle modification
- treatment of risk factors: statins (see [Endocrinology](#), E2, [Family Medicine](#), FM6 for target lipid guidelines), anti-hypertensives, etc.
- exercise program

2. Anti-platelet therapy (first line therapy)

- enteric coated ASA (ECASA)
- clopidogrel when ASA absolutely contraindicated

3. β -blockers (first line therapy – decrease overall mortality)

- increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
- cardioselective agents preferred (e.g. metoprolol, atenolol) to avoid peripheral effects (inhibition of vasodilation and bronchodilation via β_2 receptors)
- avoid intrinsic sympathomimetics (e.g. acebutolol) which increase demand

4. Nitrates (symptomatic control, no clear impact on survival)

- decrease preload (venous dilatation) and afterload (arteriolar dilatation), and increase coronary perfusion
- maintain daily nitrate-free intervals to prevent tolerance (tachyphylaxis)

5. Calcium channel blockers (CCBs, second line or combination)

- increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
- caution: verapamil/diltiazem combined with beta-blockers may cause symptomatic sinus bradycardia or AV block

6. ACE inhibitors (ACEIs, not used to treat symptomatic angina)

- angina patients tend to have risk factors for CV disease which warrant use of an ACEI (e.g. hypertension, diabetes, proteinuric renal disease, previous MI with LV dysfunction)
- class IIa evidence of benefit in all patients at high risk for CV disease
- class I evidence in patients with concomitant DM, renal dysfunction or LV systolic dysfunction
- angiotensin II receptor blockers (ARBs) when ACEIs contraindicated (e.g. hypersensitivity, angioedema)

7. Invasive Strategies

- revascularization (see *Coronary Revascularization* and *COURAGE trial*)

VARIANT ANGINA (Prinzmetal's Angina)

- myocardial ischemia secondary to coronary artery vasospasm, with or without atherosclerosis
- uncommonly associated with infarction or LV dysfunction
- typically occurs between midnight and 8 AM, unrelated to exercise, relieved by nitrates
- typically ST elevation on ECG
- diagnosed by provocative testing with ergot vasoconstrictors (rarely done)
- treat with nitrates and CCBs

SYNDROME X

- typical symptoms of angina but normal angiogram
- may show definite signs of ischemia with exercise testing
- thought to be due to inadequate vasodilator reserve of coronary resistance vessels
- better prognosis than overt epicardial atherosclerosis

Acute Coronary Syndromes (ACS)

Definition

- coronary atherosclerosis with superimposed thrombus on ruptured plaque
- other causes of unstable angina:
 - coronary thromboembolism (e.g. infective endocarditis, intracavity thrombus, paradoxical embolism) or cholesterol embolism
 - severe coronary vasospasm
 - coronary dissection
 - increased demand can also contribute (e.g. tachycardia, anemia)

Spectrum of ACS

- unstable angina (UA)/non-ST elevation myocardial infarction (NSTEMI)
- ST elevation myocardial infarction (STEMI)
- sudden cardiac death

Investigations

- history and physical
 - note that up to 30% of MIs are unrecognized or “silent” due to atypical symptoms – more common in women, DM, elderly, post-heart transplant (because of denervation)
- ECG, CXR
- labs
 - serum cardiac biomarkers for myocardial damage (repeat 8 hours later) (see *Cardiac Biomarkers*, C9)
 - CBC, INR/aPTT, electrolytes and magnesium, creatinine, urea, glucose, serum lipids
 - draw serum lipids within 24-48 hours because values are unreliable from 2 to 48 days post-MI

Is This Patient Having a Myocardial Infarction? JAMA 1998; 280:1256-63

The most compelling features that increase the likelihood of MI are ST-segment elevation, new Q-wave, chest pain radiating to both the right and left arm simultaneously, presence of an S3 and hypotension.

The most compelling features that decrease the likelihood of MI are normal ECG report, pleuritic chest pain, pain reproduced on palpation, sharp or stabbing chest pain, and positional chest pain.

Unstable Angina (UA)/Non ST Elevation MI (NSTEMI)

Definition

- syndrome of acute plaque rupture and thrombosis with incomplete or transient vessel occlusion
- unstable angina** is clinically defined by any of the following:
 - accelerating pattern of pain: increased frequency, increased duration, with decreased exertion, decreased response to treatment
 - angina at rest
 - new onset angina
 - angina post-MI or post-procedure (e.g. percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG])
- NSTEMI is clinically defined by the presence of 2 of 3 criteria:
 - symptoms of angina/ischemia
 - rise and fall of serum markers of myocardial necrosis
 - evolution of ischemic ECG changes (without ST elevation or new LBBB)
- acute phase of UA/NSTEMI**
 - risk of progression to MI or the development of recurrent MI or death is highest in the early period
 - at 1 to 3 months after the acute phase, most patients resume a clinical course similar to that in patients with chronic stable coronary disease
- majority of NSTEMIs do not result in the development of Q waves

TIMI Risk Score for UA/NSTEMI

Characteristics	Points
Historical	
Age ≥ 65 yrs	1
≥ 3 risk factors for CAD	1
Known CAD (stenosis $\geq 50\%$)	1
Aspirin use in past 7 days	1
Presentation	
Recent (≤ 24 hr) severe angina	1
ST-segment deviation ≥ 0.5 mm	1
increased cardiac markers	1
Risk Score = Total Points	
If TIMI risk score ≥ 3 , consider early LMWH and angiography	
CAD = coronary artery disease	
NSTEMI = non ST-segment elevation myocardial infarction	
TIMI = thrombolysis in myocardial infarction	
UA = unstable angina	
JAMA 2000; 284:835-842	

ST Elevation Myocardial Infarction (STEMI)

Definition

- syndrome of acute plaque rupture and thrombosis with total coronary occlusion resulting in myocardial necrosis
- STEMI is clinically defined by new ischemic ECG changes plus one or both of ischemic symptoms and elevated cardiac enzymes
 - ECG criteria (see *Approach to ECGs*, C5)
 - ST elevation in 2 contiguous leads (≥ 1 mm in limb leads or ≥ 2 mm in precordial leads) or new BBB (either LBBB or RBBB)

Acute Management of STEMI

- after diagnosis of STEMI is made, do not wait for results of further investigations before implementing reperfusion therapy
- goal is to re-perfuse artery: thrombolysis (EMS-to-needle) within **30 minutes** or primary PCI (EMS-to-balloon) within **90 minutes** (depending on capabilities of hospital)



Treatment of NSTEMI

BEMOAN
 β -blocker
 Enoxaparin
 Morphine
 O₂
 ASA
 Nitrates

Enoxaparin versus Unfractionated Heparin with Fibrinolysis for ST-elevation Myocardial Infarction

NEJM 2006; 354:1477-88

Study: Prospective, randomized, controlled multicentre trial.

Patients: 20,479 patients (median age 60 yrs. 77% male) with STEMI who were scheduled to undergo fibrinolysis.

Intervention: Patients were randomized to receive either enoxaparin or weight based unfractionated heparin in addition to thrombolysis and standard therapies.

Primary Outcome: Death or recurrent nonfatal MI 30 days post-event.

Results: The composite primary outcome occurred less often in the enoxaparin group compared with those who received unfractionated heparin (9.9% vs. 12.0%, $p < 0.001$, NNT=47). Taken separately, there was a trend toward reduced mortality (6.9% vs. 7.5%, $p = 0.11$) and a significant reduction in nonfatal reinfarction (3.0% vs. 4.5%, $p < 0.001$) in the enoxaparin group. The risk of major bleeding was significantly increased in the enoxaparin group (2.1% vs. 1.4%, $p < 0.001$, NNH=142).

Conclusion: In patients with STEMI receiving thrombolysis, enoxaparin is superior to unfractionated heparin in preventing recurrent nonfatal MI and may lead to a small reduction in mortality.

MANAGEMENT OF ACUTE CORONARY SYNDROMES

1. General measures

- ABCs: assess and correct hemodynamic status first
- bed rest, cardiac monitoring, oxygen
- nitroglycerin SL followed by IV
- morphine IV

2. Anti-platelet and anticoagulation therapy

- ASA 162-325 mg chewed
- **NSTEMI**
 - ♦ clopidogrel 300 mg loading dose, then 75 mg QD in addition to ASA or if ASA contraindicated
 - ♦ subcutaneous Low Molecular Weight Heparin or IV unfractionated heparin (UFH) (LMWH preferable, except in renal failure or if CABG is planned within 24h)
- if PCI is planned: clopidogrel 300 mg loading dose and IV GP IIb/IIIa inhibitor (e.g. abciximab)
- anticoagulation options depend on reperfusion strategy:
 - ♦ primary PCI: UFH during procedure; bivalirudin possible alternative
 - ♦ thrombolysis: LMWH (enoxaparin) until discharge from hospital; can use UFH as alternative because of possible rescue PCI
 - ♦ no re-perfusion: LMWH (enoxaparin) until discharge from hospital
- continue LMWH or UFH followed by oral anticoagulation at discharge if at high risk for thromboembolic event (large anterior MI, AFib, severe LV dysfunction, CHF, previous DVT or PE, or echo evidence of mural thrombus)

3. Beta-blockers

- first dose IV followed by oral administration
- non-dihydropyridine CCB (e.g. diltiazem, verapamil) in absence of severe LV dysfunction in patients with continuing or frequently recurring ischemia when beta-blockers are contraindicated (evidence suggests that CCBs do not prevent MI or decrease mortality)
- **STEMI:** if bradycardia is present, consider administering atropine (increased mortality in patients with hemodynamic compromise with early IV beta-blockers)

4. Invasive strategies and reperfusion options

- **UA/NSTEMI:** early coronary angiography ± revascularization if possible is recommended with any of the following high-risk indicators (class I):
 - ♦ recurrent angina/ischemia at rest despite intensive anti-ischemic therapy
 - ♦ CHF or LV dysfunction
 - ♦ hemodynamic instability
 - ♦ high (≥ 3) TIMI risk score (tool used to estimate mortality following an ACS)
 - ♦ sustained ventricular tachycardia
 - ♦ dynamic ECG changes
 - ♦ high-risk findings on non-invasive stress testing
 - ♦ PCI within the previous 6 months
 - ♦ repeated presentations for ACS despite treatment and without evidence of ongoing ischemia or high risk features (class IIa)
- **note: thrombolysis is NOT administered for UA/NSTEMI**
- **STEMI**
 - ♦ Percutaneous Coronary Intervention (PCI)
 - early PCI (≤ 12 hrs after symptom onset and < 90 mins after presentation) improves mortality vs. thrombolysis with fewer intra-cranial hemorrhages and re-current MIs
 - primary PCI: without prior thrombolytic therapy – method of choice for re-perfusion in experienced centres (JAMA 2004; 291:736-39)
 - rescue PCI: following failed thrombolytic therapy (diagnosed when, following thrombolysis, ST segment elevation fails to resolve below half its initial magnitude and patient still having chest pain)
 - ♦ Thrombolysis
 - preferred if patient presents ≤ 12 hrs of symptom onset, and < 30 min after presentation to hospital, has contraindications to PCI, or PCI cannot be administered within 90 min by a skilled practitioner

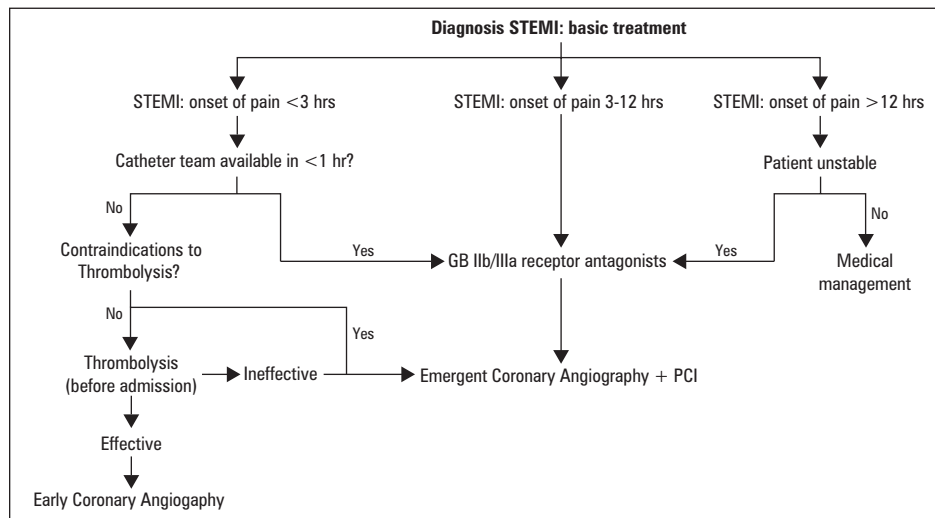


Figure 30. Reperfusion Strategy in STEMI

Table 7. Contraindications and Cautions for Thrombolysis in STEMI

Absolute	Relative
Prior intracranial hemorrhage	Chronic, severe, poorly controlled hypertension
Known structural cerebral vascular lesion	Uncontrolled hypertension (sBP>180, dBP>110)
Known malignant IC neoplasm	Current anticoagulation
Significant closed-head or facial trauma (≤3 months)	Noncompressible vascular punctures
Ischemic stroke (≤3 months)	Ischemic stroke (≥3 months)
Active bleeding	Recent internal bleeding (≤2-4 weeks)
Suspected aortic dissection	Prolonged CPR or major surgery (≤3 weeks)
	Pregnancy
	Active peptic ulcer

Long-Term Management ACS (post-discharge)

- pre-discharge: ECG (if not fully revascularized) and echo
- drugs required in hospital to control ischemia should be continued after discharge in all patients (class IIa) including patients with LV dysfunction, CHF, and diabetics (class I) and all patients who did not undergo revascularization

1. General Measures

- education
- risk factor modification

2. Anti-platelet and Anti-Coagulation Therapy

- ECASA 81-162 mg QD
- clopidogrel 75 mg QD (at least 1 month, up to 9-12 months, if stent placed at least 12 months)
- ± warfarin x 3 months if high risk (large anterior MI, LV thrombus, LVEF <30%, history of VTE, chronic AF)

3. Beta-Blockers (e.g. metoprolol 25-50 mg bid or atenolol 50-100 mg QD)**4. Nitrates**

- alleviate ischemia but do not improve outcome
- use caution in right-sided MI patients who are preload dependent

5. Calcium Channel Blockers (NOT recommended as first line treatment, consider as alternative to beta-blockers)**6. Angiotensin-Converting Enzyme Inhibitors (ACEI)**

- prevent adverse ventricular remodelling
- recommended for asymptomatic patients, even if LVEF >40%
- recommended for symptomatic CHF, reduced LVEF (<40%), anterior MI
- use ARBs in patients who are intolerant of ACEIs

7. ± Aldosterone Antagonists

- if on ACEI and beta-blockers and LVEF <40% and CHF or DM
- significant mortality benefit shown with eplerenone by 30 days

8. Statins (early, intensive, irrespective of cholesterol level; e.g. atorvastatin 80 mg QD)**9. Invasive** (risk stratification, see Figure 31)

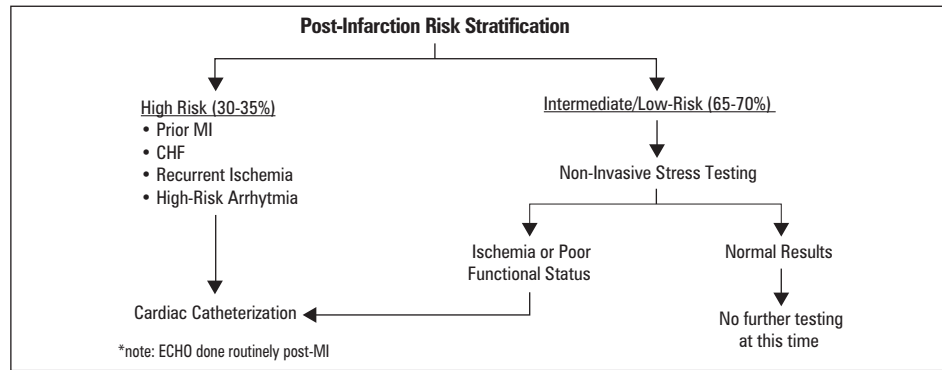


Figure 31. Post-MI Risk Stratification



Resting LVEF is a useful prognostic factor.

Prognosis following STEMI

- 5-15% of hospitalized patients will die
 - risk factors
 - ♦ infarct size/severity
 - ♦ age
 - ♦ co-morbid conditions
 - ♦ development of heart failure or hypotension
- post-discharge mortality rates
 - 6-8% within first year, half of these within first 3 months
 - 4% per year following first year
 - risk factors
 - ♦ LV dysfunction
 - ♦ residual myocardial ischemia
 - ♦ ventricular arrhythmias
 - ♦ history of prior MI

Table 8. Complications of Myocardial Infarction

Complication	Etiology	Presentation	Therapy
Arrhythmia			
1. Tachycardia	Sinus, AF, VT, VFib	First 48 hrs	See <i>Arrhythmias</i> , C12
2. Bradycardia	Sinus, AV block	First 48 hrs	
Myocardial Rupture			
1. LV free wall	Transmural infarction	1-7 days	Surgery
2. Papillary muscle (→ MR)	Inferior infarction	1-7 days	Surgery
3. Ventricular septum (→ VSD)	Septal infarction	1-7 days	Surgery
Shock/CHF	Infarction or aneurysm	Within 48 hours	Inotropes, intra-aortic balloon pump
Post-Infarct Angina	Persistent coronary stenosis multivessel disease	Anytime	Aggressive medical therapy PCI or CABG
Recurrent MI	Reocclusion	Anytime	See above
Thromboembolism	Mural/apical thrombus DVT	7-10 days, up to 6 months	Anticoagulation
Pericarditis	Inflammatory	1-7 days	ASA
(Dressler's syndrome)	Autoimmune	2-8 weeks	



Complications of MI

CRASH PAD

Cardiac Rupture

Arrhythmia

Shock

Hypertension/Heart failure

Pericarditis/Pulmonary emboli

Aneurysm

DVT

Treatment Algorithm for Chest Pain

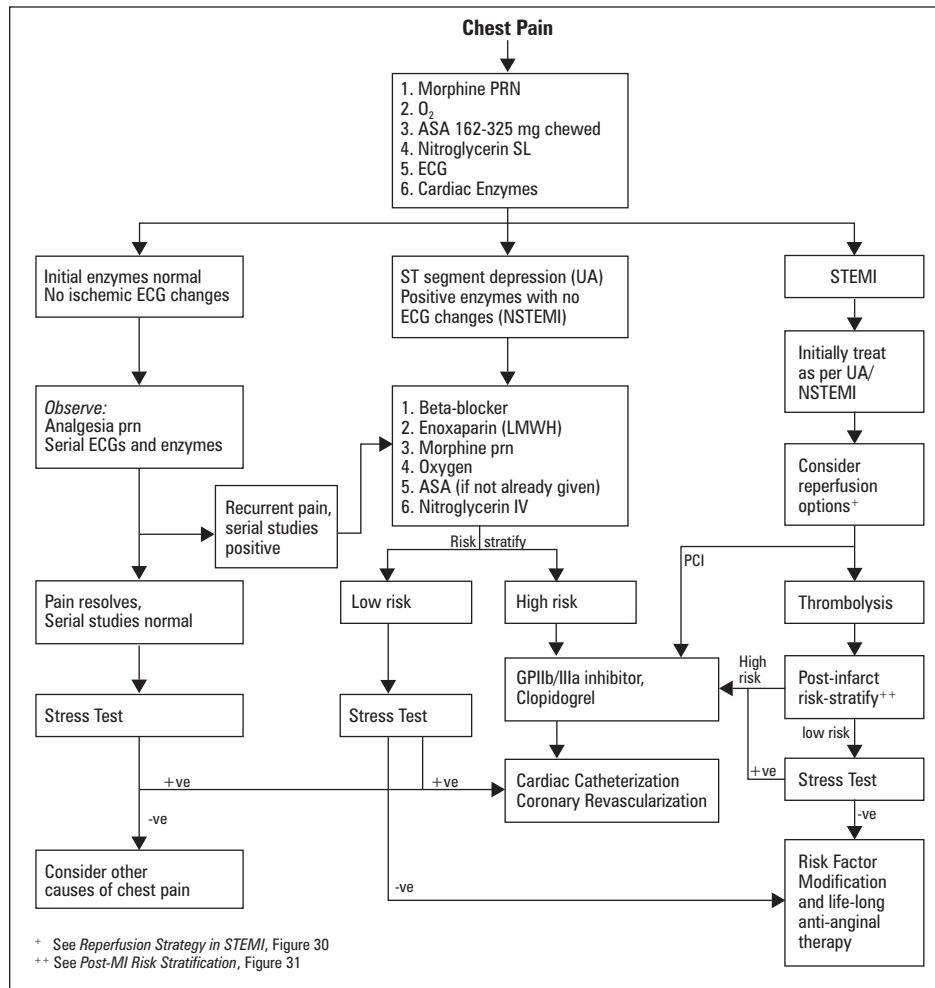


Figure 32. Treatment Algorithm for Chest Pain

Adapted from Cecil Essentials of Medicine 6th Ed. Andreoli and Carpenter. p.101 (2004) with permission from Elsevier

Sudden Cardiac Death

Definition

- unanticipated, non-traumatic cardiac death in stable patient, within 1 hour of symptom onset; ventricular fibrillation is most common cause

Etiology

- primary cardiac pathology
 - ischemia/MI
 - LV dysfunction
 - severe ventricular hypertrophy
 - ♦ hypertrophic cardiomyopathy (HCM)
 - ♦ AS
 - long QT syndrome
 - congenital heart disease

Management

- acute: resuscitate with prompt CPR and defibrillation
- investigate underlying cause (cardiac catheterization, electrophysiologic studies)
- treat underlying cause
- anti-arrhythmic drug therapy: amiodarone, beta-blockers
- implantable cardioverter defibrillator (ICD)

Percutaneous Coronary Intervention (PCI)

Safety and Efficacy of Drug-Eluting and Bare Metal Stents

Circulation 2009; 119:3198-3206

Study: Meta-analysis of RCTs and observational studies. 22 RCTs and 34 observational studies.

Population: 9,470 and 182,901 patients in RCTs and observational studies respectively who underwent percutaneous coronary intervention.

Intervention: Drug-Eluting Stents (DES) versus Bare Metal Stents (BMS).

Outcome: All-cause mortality, myocardial infarction (MI), and target vessel revascularization (TVR).

Results: No difference in mortality was found between DES vs. BMS by RCTs, while observational studies showed significantly lower mortality rates in DES-treated patients (hazard ratio (HR) 0.78, $p < 0.001$). No difference in MI incidence was found in RCTs, while lower incidences of MI were found in observational studies (HR 0.87, $p = 0.014$). DES has a significantly lower TVR rate in both RCT (HR 0.45, $p < 0.001$) and observational studies (HR 0.46, $p < 0.001$).

Conclusions: DES significantly reduces rates of TVR compared to BMS. Although there is no difference in mortality or MI incidence as found by RCTs, observational studies suggest lowered mortality and MI rates in patients with DES over BMS.

- interventional technique aimed at relieving significant coronary stenosis
- main techniques: balloon angioplasty, stenting
- less common techniques: rotational/directional/extraction atherectomy

Indications

- medically refractory angina
- NSTEMI/UA with high TIMI risk score within 90 min of presentation
- primary/rescue PCI for STEMI

Balloon Angioplasty and Intracoronary Stenting

- coronary lesions dilated with balloon inflation
- major complication is restenosis, felt to be due to elastic recoil and neointimal hyperplasia
- majority of patients receive intracoronary stent(s) to prevent restenosis
 - bare metal stent (BMS)
 - ♦ coated with antiproliferative drugs (sirolimus, paclitaxel)
 - ♦ reduced rate of neointimal hyperplasia and restenosis compared to BMS (5% vs. 20%)
 - ♦ complication: late stent thrombosis (5 events in 1000 stents implanted)

Adjunctive Therapies

- ASA and heparin decrease post-procedural complications
- further reduction in ischemic complications has now been demonstrated using GPIIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) in coronary angiography and stenting
- following stent implantation
 - dual antiplatelet therapy (ASA and clopidogrel) for 1 month with BMS or ≥ 12 months with DES

Procedural Complications

- mortality and emergency bypass rates $< 1\%$
- nonfatal MI: approximately 2-3%

Table 9. Choice of Revascularization Procedure

	PCI	CABG
Advantages	<ul style="list-style-type: none"> • Less invasive technique • Less periprocedural morbidity and mortality • Shorter periprocedural hospitalization 	<ul style="list-style-type: none"> • Greater ability to achieve complete revascularization • Less need for repeated revascularization procedures
Indications	<ul style="list-style-type: none"> • Single or double-vessel disease • Inability to tolerate surgery 	<ul style="list-style-type: none"> • Triple-vessel or left main disease • Diabetes mellitus • Plaque morphology unfavourable for PCI

Coronary Artery Bypass Graft (CABG) Surgery

- the objective of CABG is complete reperfusion of the myocardium; goals include relieving symptoms (angina, heart failure) and thus improving quality of life, and/or prolonging life

Indications

- Class I recommendations
 - CABG
 - ♦ significant left main artery disease
 - ♦ triple vessel disease, survival benefit greatest in patients with abnormal LV function (EF $< 50\%$)
 - ♦ two-vessel disease with significant proximal left anterior descending (LAD) disease and with abnormal LV function (EF $< 50\%$) or demonstrable ischemia on noninvasive testing
 - ♦ one or two vessel disease without significant LAD disease who have survived sudden cardiac death or sustained VT
 - CABG or PCI
 - ♦ patients with one or two vessel disease without significant LAD disease but with a large area of viable myocardium and high risk criteria on noninvasive testing
 - ♦ recurrent stenosis associated with a large area of viable myocardium or high risk criteria on noninvasive testing
- Class II recommendations
 - CABG or PCI
 - ♦ one vessel disease with significant proximal LAD
 - ♦ repeat CABG for multiple saphenous vein graft stenosis, with high risk criteria on noninvasive testing, especially when LAD graft at risk. PCI may be appropriate for focal lesions, or multiple lesions in poor surgical candidates
 - ♦ one or two vessel disease without significant proximal LAD disease but with a moderate area of viable ischemia on noninvasive testing

Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease. SYNTAX trial

NEJM 2009; 360(10):961-972

Study: Prospective, randomized controlled trial.

Population: 1800 patients with untreated three-vessel or left main coronary artery disease and anatomically equivalent for both Percutaneous Intervention (PCI) and Coronary Artery Bypass Graft (CABG).

Intervention: PCI versus CABG.

Outcome: Composite of death from any cause, stroke, myocardial infarction, or repeat revascularization in 12 months post-intervention.

Results: Incidence of primary outcome was lower in the CABG intervention vs. PCI (12.4% vs. 17.8%, $P = 0.002$, NNT = 19). PCI was associated with significantly higher rates of repeat revascularization (13.5% vs. 5.9%, $P < 0.001$) and cardiac death (3.7% vs. 2.1%, $P = 0.05$), while CABG had higher rates of stroke (2.2% vs. 0.6%, $P = 0.03$).

Conclusions: In patients with three-vessel or left main coronary artery disease, CABG is superior to PCI in preventing major adverse cardiovascular and cerebrovascular events within 12 months of intervention.

Operative Issues

- isolated proximal disease in large coronary arteries (>1.0-1.5 mm) is ideal for bypass surgery; small, diffusely diseased coronary arteries are not suitable for bypass surgery
- arteries with severe stenoses (>50% diameter reduction) are bypassed, except those of small calibre (<1 mm in diameter)

Table 10. Risk Factors for CABG Mortality and Morbidity

Risk Factors for CABG Mortality (decreasing order of significance)	Risk Factors for CABG Postop Morbidity or Length of Stay (decreasing order of significance)
<ul style="list-style-type: none"> Urgency of surgery (emergent or urgent) Reoperation Older age Poor left ventricular function (see below) Female gender Left main disease Others include catastrophic conditions (cardiogenic shock, ventricular septal rupture, ongoing CPR), dialysis-dependent renal failure, end-stage COPD, diabetes, cerebrovascular disease, and peripheral vascular disease 	<ul style="list-style-type: none"> Reoperation Emergent procedure Preoperative intra-aortic balloon pump (IABP) Congestive heart failure CABG + valve surgery Older age Renal dysfunction COPD Diabetes Cerebrovascular disease

- left ventricular (LV) function is an important determinant of outcome of all heart diseases
- patients with severe LV dysfunction usually have poor prognosis, but surgery can sometimes dramatically improve LV function
- assess viability of non-functioning myocardial segments using delayed thallium myocardial imaging, PET scanning or MRI

Table 11. Conduits for CABG

Graft	Occlusion/Patency Rate	Considerations
Saphenous Vein Grafts (SVG)	At 10 years, 50% occluded, 25% stenotic, 25% angiographically normal	<ul style="list-style-type: none"> Used when arterial grafts are not available or many grafts are required, such as triple or quadruple bypass
Left Internal Thoracic/Mammary Artery (LITA/LIMA) (LIMA to LAD)	90-95% patency at 15 years	<ul style="list-style-type: none"> Most preferred option because of excellent patency Improved event-free survival (angina, MI) Decreased late cardiac events No increase in operative risk
Right Internal Thoracic/Mammary Artery (RITA/RIMA)	Pedicled RIMA patency comparable to LIMA free RIMA patency less	<ul style="list-style-type: none"> Used in bilateral ITA grafting Patients receiving bilateral ITAs have less risk of recurrent angina, late myocardial infarction, angioplasty
Radial Artery (free graft)	85-90% patency at 5 years	<ul style="list-style-type: none"> Prone to severe vasospasm postoperatively due to muscular wall
Right Gastroepiploic Artery	80-90% patency at 5 years	<ul style="list-style-type: none"> Primarily used as an in situ graft to bypass the RCA Use limited because of the fragile quality of the artery, other technical issues, increased operative time (laparotomy incision) and incisional discomfort with associated ileus
Complete Arterial Revascularization		<ul style="list-style-type: none"> For younger patients (<60 years of age) Is preferred due to longer term graft patency
Redo Bypass Grafting		<ul style="list-style-type: none"> Operative mortality 2-3 times higher than first operation 10% perioperative MI rate Reoperation undertaken only in symptomatic patients who have failed medical therapy and in whom angiography has documented progression of the disease Increased risk with redo-sternotomy secondary to adhesions which may result in laceration to aorta, RV, IMA and other bypass grafts

Off-Pump Coronary Artery Bypass (OPCAB) Surgery

- complications of CABG with cardiopulmonary bypass (CPB)
 - stroke and neurocognitive defects (microembolization of gaseous and particulate matter)
 - immunosuppression
 - systemic inflammatory response leading to:
 - myocardial dysfunction
 - renal dysfunction
 - neurological injury
 - respiratory dysfunction
 - coagulopathies

Procedure

- OPCAB avoids the use of CPB by allowing surgeons to operate on a beating heart
 - stabilization devices (e.g. Genzyme Immobilizer®) hold heart in place allowing operation while positioning devices (Medtronic Octopus® and Starfish® system) allow the surgeon to lift the beating heart to access the lateral and posterior vessels
 - procedure is safe and well tolerated by most patients; however, OPCAB surgery remains technically more demanding

Indications

- used in poor candidates for CPB who have: calcified aorta, poor LVEF, severe peripheral vascular disease (PVD), severe COPD, CRF, coagulopathy, transfusion issues (e.g. Jehovah's Witness), good target vessels, anterior/lateral wall revascularization, target revascularization in older, sicker patients
- **absolute contraindications:** hemodynamic instability, poor quality target vessels including intramyocardial vessels, diffusely diseased vessels and calcified coronary vessels
- **relative contraindications:** cardiomegaly/CHF, critical left main disease, small distal targets, recent or current acute MI, cardiogenic shock, LVEF <35%

Outcomes

- OPCAB decreases in-hospital morbidity (decreased incidence of chest infection, inotropic requirement, supraventricular arrhythmia), blood product transfusion, ICU stay, length of hospitalization, and decreased CK-MB and troponin I level
- no significant difference in terms of survival at 2 years, frequency of cardiac events (MI, PCI, CHF, recurrent angina, redo CABG) or medication usage compared to on-pump CABG

Heart Failure

Congestive Heart Failure (CHF)

Definitions

- heart failure: a complex clinical syndrome, resulting from almost any cardiac disorder that impairs the ability of the ventricle to fill with or eject blood
- forward heart failure: heart unable to maintain adequate cardiac output to meet demand and/or able to do so only by elevating filling pressure
- backward heart failure: heart unable to accommodate venous return resulting in elevated filling pressures and vascular congestion (systemic or pulmonary)
- heart failure can involve left side of heart (left heart failure), right side (right heart failure) or both (biventricular failure) (see Table 12)
- heart failure can also have components of ineffective ventricular filling (diastolic dysfunction) and/or contraction (systolic dysfunction)
- most cases associated with poor cardiac output (low-output heart failure); however, some not due to intrinsic cardiac disease but instead due to increased demand (high-output heart failure)

Pathophysiology

- primary insults (myocyte loss, overload) → pump dysfunction, which leads to:
 - remodeling (dilatation, hypertrophy)
 - neurohumoral activation → necrosis and apoptosis
- both pathways result in further damage (re-starting the cycle), edema, tachycardia, vasoconstriction, congestion
- compensatory response to myocardial stress (perpetuate disease process)
 - increased end-systolic ventricular pressure (pressure overload)
 - ♦ e.g. HTN, aortic stenosis → hypertrophy
 - increased end-diastolic ventricular volume (volume overload)
 - ♦ e.g. aortic regurgitation → cardiac dilatation
- systemic response to ineffective circulating volume
 - activation of sympathetic nervous and renin-angiotensin-aldosterone systems results in:
 - ♦ salt and water retention with intravascular expansion
 - ♦ increased heart rate and myocardial contractility
 - ♦ increased afterload

Systolic Dysfunction (impaired ventricular ejection)

- impaired myocardial contractile function → decreased ejection fraction (LVEF) and stroke volume (SV) → decreased cardiac output (CO)
- findings: apex beat displaced, S3, increased heart size on CXR, decreased LVEF, LV dilatation
- causes:
 - ischemic (e.g. extensive CAD, previous MI)
 - non-ischemic
 - ♦ hypertension
 - ♦ diabetes mellitus
 - ♦ alcohol (and other toxins)
 - ♦ myocarditis
 - ♦ dilated cardiomyopathy



Dichotomies of Heart Failure
 Forward vs. Backward
 Left-sided vs. Right-sided
 Systolic dysfunction vs. Diastolic dysfunction
 Low output vs. High output



Use Ejection Fraction to Grade LV Dysfunction
 Grade I (EF > 60%) (Normal)
 Grade II (EF = 40-59%)
 Grade III (EF = 21-39%)
 Grade IV (EF ≤ 20%)

Diastolic Dysfunction (impaired ventricular filling)

- at least 1/3 of all HF patients have normal systolic function (i.e. normal ejection fraction); prevalence higher in older patients
- increased LV filling pressures produce venous congestion upstream (i.e. pulmonary and systemic venous congestion)
- findings: HTN, apex beat sustained, S4, normal-sized heart on CXR, LVH on ECG/echo, normal LVEF
- causes of decreased compliance:
 - transient: ischemia (relaxation of myocardium is active and requires ATP)
 - permanent
 - ♦ severe hypertrophy (HTN, AS, HCM)
 - ♦ restrictive cardiomyopathy (RCM)
 - ♦ MI

High-Output Heart Failure

- caused by demand for increased cardiac output
- often exacerbates existing heart failure or decompensates a patient with other cardiac pathology
- differential diagnosis: anemia, thiamine deficiency (beriberi), hyperthyroidism, A-V fistula or L-R shunting, Paget's disease, renal disease, hepatic disease

Etiologies of Primary Insults

- consider predisposing, precipitating and perpetuating factors
- most common causes see sidebar
- less common causes of CHF
 - toxic e.g. anthracyclines, radiation, uremia, catecholamines
 - infectious e.g. Chagas' disease (common cause in South America), Coxsackie virus, HIV
 - endocrine e.g. hyperthyroidism, DM, acromegaly
 - infiltrative e.g. sarcoidosis, amyloidosis, hemochromatosis
 - genetic e.g. HCM, Friedreich's Ataxia, muscular dystrophy
 - congenital heart disease
 - metabolic e.g. thiamine deficiency, selenium deficiency
 - peripartum

Precipitants of Symptomatic Exacerbations

- consider natural progression of disease vs. new precipitant
- always search for reversible cause
- see side bar ("HEART FAILED")
- differential can also be organized as follows:
 - new cardiac insult/disease: MI, arrhythmia, valvular disease
 - new demand on CV system: hypertension, anemia, thyrotoxicosis, infection, etc.
 - failure to take medications as prescribed

Table 12. Signs and Symptoms of Left vs. Right Heart Failure

	Left Failure	Right Failure
Low cardiac output (forward)	Fatigue Syncope Systemic hypotension Cool extremities Slow capillary refill Peripheral cyanosis Pulsus alternans Mitral regurgitation S3	Right heart failure can mimic most of the symptoms of forward left heart failure if decreased RV output leads to LV underfilling
Venous congestion (backward)	Dyspnea, orthopnea, PND Cough Crackles	Tricuspid regurgitation S3 (right-sided) Peripheral edema Elevated JVP with AJR and Kussmaul's sign Hepatomegaly Pulsatile liver

Investigations

- identify and assess precipitating factors and treatable causes of CHF
- blood work: CBC, electrolytes (including calcium and magnesium), BUN, creatinine, fasting blood glucose, HbA1C, lipid profile, liver function tests, serum thyroid-stimulating hormone, \pm ferritin, BNP, uric acid (associated with prognosis of HF in Seattle HF Score)
- ECG: look for chamber enlargement, arrhythmia, ischemia/infarction
- CXR: cardiomegaly, pleural effusion, redistribution, Kerley B-lines, bronchiolar-alveolar cuffing
- echocardiography: LVEF, cardiac dimensions, wall motion abnormalities, valvular disease, pericardial effusion
- radionuclide angiography (MUGA): LVEF
- myocardial perfusion scintigraphy (thallium or sestamibi SPECT)

**New York Heart Association (NYHA) Functional Classification of Heart Failure**

- **Class I:** ordinary physical activity does not cause symptoms of HF
- **Class II:** comfortable at rest, ordinary physical activity results in symptoms
- **Class III:** marked limitation of ordinary activity; less than ordinary physical activity results in symptoms
- **Class IV:** inability to carry out any physical activity without discomfort; symptoms may be present at rest

**What are the Five Most Common Causes of CHF?**

1. Coronary artery disease (60-70%)
2. HTN
3. Idiopathic (often in the form of dilated cardiomyopathy)
4. Valvular (e.g. AS, AR and MR)
5. Alcohol (may cause dilated cardiomyopathy)

**Precipitants of Heart Failure****HEART FAILED**

- Hypertension (common)
- Endocarditis/environment (e.g. heart wave)
- Anemia
- Rheumatic heart disease and other valvular disease
- Thyrotoxicosis
- Failure to take meds (very common)
- Arrhythmia (common)
- Infection/ischemia/Infarction (common)
- Lung problems (PE, pneumonia, COPD)
- Endocrine (pheochromocytoma, hyperaldosteronism)
- Dietary indiscretions (common)



The most common cause of right heart failure is left heart failure.

**Measuring NT-pro BNP**

BNP is secreted by ventricles due to LV stretch and wall tension. Cardiomyocytes secrete BNP precursor that is cleaved into proBNP. After secretion into ventricles, proBNP is cleaved into the active C-terminal portion and the inactive NT-proBNP portion.

NT-proBNP levels (pg/mL)

Age	HF very likely
<50	>450
50-75	>900
>75	>1800

Limitations – Age, body habitus, renal function, pulmonary embolism



Features of Heart Failure on CXR

HERB-B

Heat enlargement (cardiothoracic ratio >0.50)

Effusion

Re-distribution (alveolar edema)

B-lines

Bronchiolar-alveolar cuffing

Acute Treatment of Pulmonary Edema

- treat acute precipitating factors (e.g. ischemia, arrhythmias)
- **L** – Lasix® (furosemide) 40-500 mg IV
- **M** – morphine 2-4 mg IV – decreases anxiety and preload (venodilation)
- **N** – nitroglycerin – topical/IV/SL
- **O** – oxygen
- **P** – positive airway pressure (CPAP/BiPAP) – decreases preload and need for ventilation
- **P** – position – sit patient up with legs hanging down unless patient is hypotensive
- in ICU setting or failure of LMNOP, other interventions may be necessary
 - nitroprusside (IV)
 - hydralazine (PO)
 - sympathomimetics
 - ♦ dopamine
 - low dose: selective renal vasodilation (high potency D_1 agonist)
 - medium dose: inotropic support (medium potency β_1 agonist)
 - high dose: increases SVR (low potency β_1 agonist), which is undesirable
 - ♦ dobutamine
 - selective inotrope (β_1 agonist) and arterial vasodilator (β_1 antagonist)
 - ♦ phosphodiesterase inhibitors (milrinone)
 - inotropic effect and vascular smooth muscle relaxation (decreased SVR), similar to dobutamine
 - adverse effect on survival when used as long-term oral agent
- consider PA catheter to monitor pulmonary capillary wedge pressure (PCWP) if patient is unstable or a cardiac etiology is uncertain (PCWP >18 indicates likely cardiac etiology)
- mechanical ventilation as needed
- rarely used, but potentially life-saving measures:
 - intra-aortic balloon pump (IABP)
 - left or right ventricular assist device (LVAD/RVAD)
 - cardiac transplant

Long Term Management

Conservative Measures

1. Symptomatic measures: oxygen in hospital, bedrest, elevation of head of bed
2. Lifestyle measures (grade B evidence): diet, exercise, DM control, smoking cessation, decrease alcohol consumption, patient education, sodium and fluid restriction
3. Multidisciplinary heart failure clinics (grade B evidence): for management of individuals at higher risk, or with recent hospitalization

Pharmacological Therapy

1. Vasodilators

- a. ACEIs: standard of care – slow progression of LV dysfunction and improve survival
 - ♦ all symptomatic patients functional class II-IV (grade A)
 - ♦ all asymptomatic patients with LVEF <40% (grade A)
 - ♦ post-MI
 - ♦ target dose as used in mortality trials, or maximum tolerated dose
- b. angiotensin II receptor blockers (ARBs)
 - ♦ second line to ACEI if not tolerated (grade B), or as adjunct to ACEI if beta-blockers not tolerated (grade A)
- c. hydralazine and nitrates (Ve-HeFT-I trial)
 - ♦ second line to ACEI, decrease in mortality not as great as with ACEI
 - ♦ may consider in acute renal failure until creatinine stabilizes

2. Beta-blockers: slow progression and improve survival

- class I-III with LVEF <40% (grade A)
- stable class IV patients (grade A)
- **note: should be used cautiously, titrate slowly because may initially worsen CHF**

3. Diuretics: symptom control, management of fluid overload

- furosemide (40-500 mg OD) for potent diuresis
- metolazone may be used with furosemide to increase diuresis
- furosemide, metolazone, and thiazides oppose the hyperkalemia induced by beta-blockers, ACEIs, ARBs, and aldosterone antagonists

4. Aldosterone antagonists: mortality benefit in severe CHF

- spironolactone for class IIIb and IV CHF already on ACEI and loop diuretic (grade A)
- eplerenone may be considered if intolerable endocrine side effects
- **note: potential for life threatening hyperkalemia**
 - ♦ monitor K after initiation and avoid if Cr >220 $\mu\text{mol/L}$ or K >5.2 mmol/L

Can the Clinical Examination Diagnose Left-Sided Heart Failure in Adults?

JAMA 1997; 277:1712-99

"The best findings for detecting increased filling pressure are jugular venous distention and radiographic redistribution."

"The best findings for detecting systolic dysfunction are an abnormal apical impulse, radiographic cardiomegaly, Q-waves or LBBB on an electrocardiogram."

"Diastolic dysfunction is difficult to diagnose but is associated with elevated blood pressure during heart failure."



Chronic Treatment of CHF

- ACE inhibitors*
- Beta blockers*
- \pm Aldosterone antagonists* (if severe CHF)
- Diuretic
- \pm Inotrope
- \pm Antiarrhythmic
- \pm Anticoagulant

* = Mortality Benefit



Medications Contraindicated in CHF

- NSAIDs – may increase BP
- Class I/III antiarrhythmics
- Metformin – C/I in severe HF
- Thiazolidinediones – increase edema
- cGMP phosphodiesterase inhibitors (e.g. sildenafil) with baseline low BP

5. **Inotropes:** digoxin improves symptoms and decreases hospitalizations, no effect on mortality
 - indications: patient in sinus rhythm and symptomatic on ACEI (grade A), or CHF and atrial fibrillation (grade B)
 - patients on digitalis glycosides may worsen if these are withdrawn
6. **Anti-arrhythmic drugs:** for use in CHF with arrhythmia
 - can use amiodarone, beta-blocker, or digoxin (grade B)
7. **Anticoagulants:** warfarin for prevention of thromboembolic events
 - prior thromboembolic event or atrial fibrillation (grade B), presence of LV thrombus on echo
 - possible benefit in other patients with LVEF <30% (controversial)
8. **CCBs** (equivocal effect on survival): not currently recommended

Procedural Interventions

- resynchronization therapy: symptomatic improvement with biventricular pacemaker
 - consider if QRS >130 ms, LVEF <35%, and severe symptoms despite optimal therapy (grade B)
 - greatest benefit likely with marked LV enlargement, MR, QRS >150 ms, high diuretic requirement
- ICD: mortality benefit in 1° and 2° prevention of sudden cardiac death
 - prior MI, optimal medical therapy, LVEF <30%, clinically stable (grade B)
 - prior MI, NSVT, LVEF 30-40%, EPS inducible VT (grade B)
- LVAD/RVAD (see *Ventricular Assist Devices*, C36)
- cardiac transplantation (see *Cardiac Transplantation*, C35)
- valve repair if patient is surgical candidate and has significant valve disease contributing to CHF (see *Valvular Heart Disease*, C40)

Sleep-Disordered Breathing

- 45-55% of patients with CHF have sleep disturbances, including Cheyne-Stokes breathing and sleep apnea (central or obstructive)
- associated with a worse prognosis and greater LV dysfunction
- nasal continuous positive airway pressure (CPAP) is effective in treating Cheyne-Stokes respiration/sleep apnea with improvement in cardiac function and symptoms

Cardiac Transplantation

- for end-stage heart disease; due to ischemic cardiomyopathy (60%), idiopathic cardiomyopathy (20%), and minority due to valvular or congenital problems
- worldwide 1-year survival is 79%, 5-year survival about 60%, annual mortality rate of 4%
- donor hearts are considered from patients up to age 50-55
- matching is according to blood type, body size and weight (should be within 25%), and HLA tissue matching (if time allows)

Indications for Surgery

- severe cardiac disability despite maximal medical therapy (recurrent hospitalizations for CHF, NYHA III or IV, peak metabolic oxygen consumption <14 ml/kg/min in absence of beta-blocker)
- symptomatic cardiac ischemia refractory to conventional treatment (unstable angina not amenable to CABG or angioplasty with LVEF <30%; recurrent, symptomatic ventricular arrhythmias)
- exclusion of all surgical alternatives to cardiac transplantation (revascularization for significant reversible ischemia, valve replacement for critical aortic valve disease, valve replacement or repair for severe MR)

Prerequisites

- emotionally stable with social support
- medically compliant and motivated
- contraindications: incurable malignancy, major systemic illness, irreversible major organ disease (e.g. renal, hepatic), active systemic infection (e.g. Hep C, HIV), obesity, irreversible pulmonary hypertension (pulmonary vascular resistance [PVR] >6 Wood units), severe COPD (FEV₁ <1 L), or active drug addiction or alcoholism
- typically age <70 years

Complications

- rejection
 - common, however less than 5% have serious hemodynamic compromise
 - gold standard to detect rejection: endomyocardial biopsy
 - ◆ no noninvasive tests to detect rejection
 - risk of acute rejection is greatest during the first 3 months after transplant

- infection
 - leading cause of morbidity and mortality after cardiac transplantation
 - risk peaks early during the first few months after transplantation and then declines to a low persistent rate
- allograft coronary artery disease
 - approximately 50% develop graft CAD within 5 years of transplantation
 - the most common cause of late death following transplantation
- malignancy
 - develop in 15% of cardiac transplant recipients
 - second most common cause of late death following transplantation
 - cutaneous neoplasms most common, followed by non-Hodgkin's lymphoma and lung cancer
- immunosuppressive medication side effects (prednisone, cyclosporine, tacrolimus, sirolimus)

Prognosis

- the Heart Failure Survival Score (HFSS) uses 7 prognostic variables – ischemic cardiomyopathy, resting heart rate, LVEF, mean BP, QRS >120ms, serum Na, peak VO_2 – to stratify patients into low, medium, and high risk categories; one-year survival rates without transplant for these three strata were 88, 60, and 35%, respectively

Ventricular Assist Devices (VADs)

- works to unload the ventricle while maintaining its output; also results in decreased myocardial oxygen consumption, permitting recovery of the myocardium that is not irreversibly injured
- can support the left (LVAD), right (RVAD) or both ventricles (BiVAD)
- indications
 - bridge to transplantation
 - postoperative mechanical support when unable to separate from cardiopulmonary bypass despite inotropic and Intra-Aortic Balloon Pump (IABP) support
 - ♦ IABP is a catheter based device inserted into the aorta via the femoral artery that decreases myocardial O_2 demand and increases blood flow to coronary arteries
 - postoperative cardiogenic shock

REMATCH Trial

Ann Thorac Surg 1999; 67:723-730
Increased survival of 23% vs. 8% with LVAD vs. medical management of heart failure after 2 years. Heartmate VAD has a biologic surface, therefore does not require long-term anticoagulation, but higher risk of infection.

Myocardial Disease

Definition of Cardiomyopathy (CMP)

- intrinsic or primary myocardial disease not 2° to congenital, hypertensive, coronary, valvular, or pericardial disease
- functional classification: dilated, hypertrophic or restrictive
- LV dysfunction 2° to MI often termed “ischemic cardiomyopathy”, but is not a true cardiomyopathy (i.e. primary myocardial disorder) since the primary pathology is CAD

Myocarditis

Definition

- inflammatory process involving the myocardium ranging from acute to chronic; an important cause of dilated cardiomyopathy

Etiology

- idiopathic
- infectious
 - viral (most common): coxsackie B, echovirus, poliovirus, HIV, mumps
 - bacterial: *S. aureus*, *C. perfringens*, *C. diphtheriae*, *Mycoplasma*, *Rickettsia*
 - fungi
 - spirochetal (Lyme disease – *Borrelia burgdorferi*)
 - Chagas disease (*Trypanosoma cruzi*), toxoplasmosis
- toxic: catecholamines, chemotherapy, cocaine
- hypersensitivity, eosinophilic: drugs (antibiotics, diuretics, lithium, clozapine), insect/snake bites
- systemic diseases: collagen vascular diseases (SLE, RA, others), sarcoidosis, autoimmune
- other: giant cell myocarditis, acute rheumatic fever

Signs and Symptoms

- constitutional symptoms
- acute CHF
- chest pain – due to pericarditis or cardiac ischemia
- arrhythmias
- systemic or pulmonary emboli
- sudden death

Investigations

- ECG: non-specific ST-T changes \pm conduction defects
- bloodwork
 - increased CK, troponin, LDH, and AST with acute myocardial necrosis \pm increased WBC, ESR, ANA, rheumatoid factor, complement levels
 - blood culture, viral titres and cold agglutinins for Mycoplasma
- CXR: enlarged cardiac silhouette
- echo: dilated, hypokinetic chambers, segmental wall motion abnormalities
- myocardial biopsy

Management

- supportive care
- restrict physical activity
- treat CHF
- treat arrhythmias
- anticoagulation
- treat underlying cause if possible

Prognosis

- usually self-limited and often unrecognized, many recover
- sudden death in young adults
- may progress to dilated cardiomyopathy
- few may have chronic myocarditis

Table 13. Summary Table for CHF and Myocardial Disease

SYSTOLIC HEART FAILURE			DILATOLIC HEART FAILURE	
Dilated Cardiomyopathy	Secondary Causes	Hypertrophic Cardiomyopathy	Restrictive Cardiomyopathy	Secondary Causes
Idiopathic, infectious (e.g. myocarditis), alcohol, familial, collagen vascular disease, etc.	Coronary artery disease, MI, diabetes, valvular (e.g. AR, MR)	Genetic disorder affecting cardiac sarcomeres (most common cause of sudden cardiac death in young athletes)	Amyloidosis, sarcoidosis, scleroderma, hemochromatosis, Fabry's, Pompe's Disease, Loeffler's, etc.	Hypertension, diabetes, valvular (e.g. AS), post-MI, transiently by ischemia, etc.

Dilated Cardiomyopathy (DCM)**Definition**

- unexplained dilation and impaired systolic function of one or both ventricles

Etiology

- idiopathic (presumed viral or genetic) ~50% of DCM
- alcohol
- familial
- uncontrolled tachycardia (e.g. persistent atrial fibrillation)
- collagen vascular disease: SLE, PAN, dermatomyositis, progressive systemic sclerosis
- infectious: viral (coxsackie B, HIV), Chagas disease, Lyme disease, Rickettsial diseases, acute rheumatic fever, toxoplasmosis
- neuromuscular disease: Duchenne muscular dystrophy, myotonic dystrophy, Friedreich's ataxia
- metabolic: uremia, nutritional deficiency (thiamine, selenium, carnitine)
- endocrine: hyper/hypothyroidism, DM, pheochromocytoma
- peripartum
- toxic: cocaine, heroin, organic solvents
- drugs: chemotherapies (doxorubicin, cyclophosphamide), anti-retrovirals, chloroquine, clozapine, TCA
- radiation induced

Signs and Symptoms

- may present as
 - CHF
 - systemic or pulmonary emboli
 - arrhythmias
 - sudden death (major cause of mortality due to fatal arrhythmia)



Major Risks Factors for DCM
Alcohol, cocaine, family history and obesity.

**Abnormal Labs in DCM**

High BNP
High Cr
High LFTs
Low Bicarb
Low Na

Investigations

- bloodwork: CBC, electrolytes, Cr, bicarbonate, BNP, CK, troponin, LFTs, TSH, TIBC
- ECG: variable ST-T wave abnormalities, poor R wave progression, conduction defects (e.g. BBB), arrhythmias (non-sustained VT)
- CXR: global cardiomegaly (globular heart), signs of CHF, pleural effusion
- echocardiography: chamber enlargement, global hypokinesis, depressed LVEF, MR and TR, mural thrombi
- endomyocardial biopsy: not routine, used to rule out a treatable cause
- angiography: in selected patients to exclude ischemic heart disease

Management

- treat underlying disease: e.g. abstinence from EtOH
- treat CHF: see *Heart Failure*, C32
- thromboembolism prophylaxis: anticoagulation with warfarin
 - indicated for: AF, history of thromboembolism or documented thrombus
 - LVEF <30% (controversial)
- treat symptomatic or serious arrhythmias
- immunize against influenza and *S. pneumoniae*
- consider surgical options (e.g. LVAD, transplant, volume reduction surgery) in appropriate candidates with severe, refractory disease
- consider ICD among patients with a LVEF <30%

Prognosis

- depends on etiology
 - better with reversible underlying cause, worst with infiltrative diseases, HIV, drug-induced
- cause of death usually CHF (due to pump failure) or sudden death 2° to ventricular arrhythmias
- systemic emboli are significant source of morbidity
- 20% mortality in 1st year, 10% per year after

Hypertrophic Cardiomyopathy (HCM)

Definition

- defined as unexplained ventricular hypertrophy (not due to systemic HTN or AS)
 - most causes involve asymmetric pattern of hypertrophy (septal hypertrophy most common)

Etiology and Pathophysiology

- histopathologic features include myocyte disarray, myocyte hypertrophy, and interstitial fibrosis
- cause is felt to be a genetic defect involving one of the cardiac sarcomeric proteins (>200 mutations associated with autosomal dominant inheritance, incomplete penetrance)
- prevalence of 1/500-1/1000 in general population
- presents as early as 20-40 yrs old

Hemodynamic Classification

- hypertrophic obstructive cardiomyopathy (HOCM): dynamic LV outflow tract (LVOT) obstruction, either at rest or with provocation
- non-obstructive hypertrophic cardiomyopathy: no LVOT obstruction
- many patients have diastolic dysfunction (impaired ventricular filling secondary to LV hypertrophy which decreases compliance)

Signs and Symptoms (of HCM)

- clinical manifestations: asymptomatic (common, therefore screening is important), SOB, angina, presyncope/syncope (due to LV outflow obstruction or arrhythmia), CHF, arrhythmias, sudden cardiac death (SCD)
- pulses: rapid upstroke, bifid carotid pulse (in HOCM)
- precordial palpation: PMI localized, sustained, double impulse, 'triple ripple' (triple apical impulse in HOCM), LV lift
- precordial auscultation: normal or paradoxically split S2, S4, harsh systolic diamond-shaped murmur at LLSB or apex, enhanced by squat to standing or Valsalva (murmur secondary to LVOT obstruction as compared to aortic stenosis); often with pansystolic murmur due to mitral regurgitation

Investigations

- ECG: LVH, high voltages across precordium, prominent Q waves (lead I, aVL, V5, V6), tall R wave in V1, P wave abnormalities
- echo: asymmetric septal hypertrophy (less commonly apical), systolic anterior motion of mitral valve and MR
- cardiac catheterization (usually performed only when patient being considered for invasive therapy)

Management

- avoid factors which increase obstruction, including volume depletion and strenuous exertion
- treatment of HOCM (with LVOT obstruction)
 - medical agents: beta-blockers, disopyramide, verapamil (only in patients without resting or provokable obstruction)
 - avoid nitrates, diuretics and ACEI as they decrease outflow tract diameter and worsen symptoms
- patients with drug-refractory symptoms
 - surgical myectomy
 - septal ethanol ablation
 - dual chamber pacing
- treatment of ventricular arrhythmias: amiodarone or ICD
- first-degree relatives of patients with HCM should be screened annually during adolescence (physical, ECG, 2D echo), then serially every 5 years

Prognosis

- potential complications: AF, VT, CHF, sudden death (most common cause of SCD in young athletes)
- major risk factors for sudden death (consider ICD placement)
 - history of survived cardiac arrest/sustained VT
 - family history of multiple premature sudden deaths
 - other factors associated with increased risk of sudden cardiac death
 - ♦ syncope
 - ♦ non-sustained VT on ambulatory monitoring
 - ♦ marked ventricular hypertrophy (maximum wall thickness ≥ 30 mm)
 - ♦ abnormal BP in response to exercise (in young patients with HCM)

Restrictive Cardiomyopathy (RCM)

Definition

- impaired ventricular filling with usually intact systolic function in a non-dilated, non-hypertrophied ventricle 2° to myocardial abnormality (stiffening, fibrosis and/or decreased compliance)
- usually with intact systolic function initially

Etiology

- infiltrative: amyloidosis, sarcoidosis
- non-infiltrative: scleroderma, idiopathic myocardial fibrosis
- storage diseases: hemochromatosis, Fabry's disease, Gaucher's disease, glycogen storage diseases
- endomyocardial
 - endomyocardial fibrosis, Loeffler's endocarditis or eosinophilic endomyocardial disease
 - radiation heart disease
 - carcinoid syndrome (may have associated TV or PV dysfunction)

Clinical Manifestations

- CHF (usually with preserved LV systolic function), arrhythmias
- elevated JVP with prominent x and y descents, Kussmaul's sign
- S3, S4, MR, TR
- thromboembolic events

Investigations

- ECG: low voltage, non-specific, diffuse ST-T wave changes \pm non-ischemic Q waves
- CXR: mild cardiac enlargement
- echo: LAE, RAE; specific Doppler finding with no significant respiratory variation
- cardiac catheterization: increased end-diastolic ventricular pressures
- endomyocardial biopsy: to determine etiology (especially for infiltrative RCM)

Management

- exclude constrictive pericarditis
- treat underlying disease: control HR, anticoagulate if atrial fibrillation
- supportive care and treatment for CHF, arrhythmias
- heart transplant: might be considered for CHF refractory to medical therapy

Prognosis

- depends on etiology

Valvular Heart Disease

Infective Endocarditis (IE)

- see [Infectious Diseases](#), ID14
- AHA 2007 guidelines recommend IE prophylaxis
 - only for patients with prosthetic valve material, past history of IE, certain types of congenital heart disease or cardiac transplant recipients who develop valvulopathy
 - only for the following procedures
 - ♦ dental
 - ♦ respiratory tract
 - ♦ procedures on infected skin/skin structures/MSK structures
 - ♦ **not GI/GU procedures specifically**

Rheumatic Fever

- see [Pediatrics](#), P57

Prognosis

- acute complications: myocarditis (DCM/CHF), conduction abnormalities (sinus tachycardia, AF), valvulitis (acute MR), acute pericarditis (not constrictive pericarditis)
- chronic complications: rheumatic valvular heart disease – fibrous thickening, adhesion, calcification of valve leaflets resulting in stenosis/regurgitation, increased risk of IE ± thromboembolism
- onset of symptoms usually after 10-20 year latency from acute carditis of rheumatic fever
- mitral valve most commonly affected

Choice of Valve Prosthesis

A Bedside Clinical Prediction Rule for Detecting Moderate or Severe Aortic Stenosis

Etchells E, Glenns V, Shadowitz S, Bell C, Siu S. *J Gen Intern Med* 1998; 13(10):699-704. Department of Medicine, Toronto Hospital, ON, Canada.

Type: Blinded cross sectional study.

Who: 124 patients of an ambulatory cardiology clinic. Patients were examined for: 1) murmur over the right clavicle 2) murmur loudest at second right intercostal space 3) reduced intensity of S2 4) reduced volume of the carotid pulse 5) delayed carotid upstroke.

Methods: Patients were examined by blinded investigators, and the clinical examination findings were compared to findings on subsequent echocardiography. Moderate to severe aortic stenosis was defined as a valve area $<1.2 \text{ cm}^2$ or a peak intensity gradient of $>25 \text{ mmHg}$.

Results: Absence of a murmur over the right clavicle ruled out aortic stenosis while presence of ≥ 3 of the 4 associated symptoms ruled in aortic stenosis (LR=40).

Conclusions: Bedside techniques can accurately rule in and rule out moderate to severe aortic stenosis.

Table 14. Mechanical Valve vs. Bioprosthetic Valve

Mechanical Valve	Bioprosthetic Valve
<ul style="list-style-type: none"> • Good durability • Less preferred in small aortic root (stenotic) • Increased risk of thromboembolism (1-3%/year): long-term anticoagulation with coumadin • Target INR aortic valves: 2.0-3.0 mitral valves: 2.5-3.5 • Increased risk of hemorrhage: 1-2%/year 	<ul style="list-style-type: none"> • Limited long-term durability (mitral < aortic) • Good flow in small aortic root sizes • Decreased risk of thromboembolism: long-term anticoagulation not needed for aortic valves • Some recommendation for limited anticoagulation for mitral valves • Decreased risk of hemorrhage

Summary of Valvular Disease

Table 15. Valvular Heart Disease

AS

Etiology

Congenital (bicuspid, unicuspid valve), calcification (wear and tear), rheumatic disease

Aortic valve area: $N=3-4 \text{ cm}^2$

Mild AS $1.5 \text{ to } 3 \text{ cm}^2$

Moderate AS $1.0 \text{ to } 1.5 \text{ cm}^2$

Severe AS $<1.0 \text{ cm}^2$

Critical AS $<0.5 \text{ cm}^2$

Pathophysiology

Outflow obstruction \rightarrow increased EDP \rightarrow concentric LVH \rightarrow LV failure \rightarrow CHF, subendocardial ischemia

Symptoms

Exertional angina, syncope, dyspnea, PND, orthopnea, peripheral edema

Physical Exam

Narrow pulse pressure, brachial-radial delay, pulsus parvus et tardus, sustained PMI
Auscultation: crescendo-decrescendo SEM radiating to R clavicle and carotid, musical quality at apex (Gallavardin phenomenon), S₄, soft S₂ w/paradoxical splitting, S₃ (late)

Investigations

ECG: LVH and strain, LBBB, LAE, AF

CXR: post-stenotic aortic root dilatation, calcified valve, LVH, LAE, CHF

ECHO: reduced valve area, pressure gradient, LVH, reduced LV function

Treatment

Asymptomatic: serial Echos, avoid exertion

Symptomatic: avoid nitrates/arterial dilators and ACEIs in severe AS

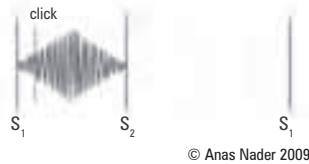
Surgery if: symptomatic or LV dysfunction

Surgical Options

Valve replacement: aortic rheumatic valve disease and trileaflet valve

– Pregnancy

– Balloon valvuloplasty (in very young)



AR

Etiology

Supravalvular: aortic root disease (Marfan's, atherosclerosis and dissecting aneurysm, connective tissue disease)

Valvular: congenital (bicuspid AV, large VSD), IE

Acute Onset: IE, aortic dissection, trauma, failed prosthetic valve

Pathophysiology

Volume overload \rightarrow LV dilatation \rightarrow increased SV, high sBP and low dBP \rightarrow increased wall tension \rightarrow pressure overload \rightarrow LVH (low dBP \rightarrow decreased coronary perfusion)

Symptoms

Usually only becomes symptomatic late in disease when LV failure develops

Dyspnea, orthopnea, PND, syncope, angina

Physical Exam

Waterhammer pulse, bisferiens pulse, femoral-brachial sBP >20 (Hill's test wide pulse pressure), hyperdynamic apex, displaced PMI, heaving apex

Auscultation: early decrescendo diastolic murmur at LLSB (cusp) or RLSB (aortic root), best heard sitting, leaning forward, on full expiration, soft S₁, absent S₂, S₃ (late)

Investigations

ECG: LVH, LAE

CXR: LVH, LAE, aortic root dilatation

Echo/TTE: quantify AR, leaflet or aortic root anomalies

Cath: if >40 yrs and surgical candidate – to assess for ischemic heart disease

Exercise testing: hypotension with exercise

Treatment

Asymptomatic: serial Echos, afterload reduction (e.g. ACEIs, nifedipine, hydralazine)

Symptomatic: avoid exertion, treat CHF

Surgery if: NYHA class III-IV CHF, LVEF $<50\%$ with/without symptoms, increasing LV size

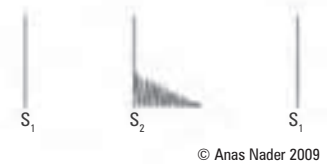
Surgical Options

Valve replacement: most patients

Valve repair: very limited role

Aortic root replacement (Bentall procedure):

– When ascending aortic aneurysm present, valved conduit used



MS

Etiology

Rheumatic disease most common cause; congenital (rare)

Severe MS is MVA $<1.2 \text{ cm}^2$

Pathophysiology

MS \rightarrow fixed CO and LAE \rightarrow increased LA pressure \rightarrow pulmonary vascular resistance and CHF; worse with AF (no atrial kick), tachycardia (decreased atrial emptying time) and pregnancy (increased preload)

Symptoms

SOBOE, orthopnea, fatigue, palpitations, peripheral edema, malar flush, pinched and blue facies (severe MS)

Physical Exam

AF, no "a" wave on JVP, left parasternal lift, palpable diastolic thrill at apex

Auscultation: mid-diastolic rumble at apex, best with bell in LLD position following exertion, loud S₁, OS following loud P₂ (heard best during expiration), long murmur and short A2-OS interval correlate with worse MS

Investigations

ECG: NSR/AF, LAE (P mitrale), RVH, RAD

CXR: LAE, CHF, MV calcification

Echo/TTE: restricted opening of MV

Cath: concurrent CAD if >40 yrs (male) or >50 yrs (female)

Treatment

Avoid exertion, fever (increased LA pressure), treat AF and CHF, increase diastolic filling time (beta-blockers, digitalis)

Surgery if: NYHA class III-IV CHF and failure of medical therapy (usually MVA $<1.2 \text{ cm}^2$)

Invasive Options

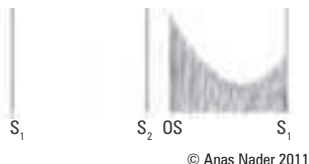
Percutaneous balloon valvuloplasty: young rheumatic pts and good leaflet morphology, asymptomatic pts with mod-sev MS, new-onset AF, pulmon HTN

Contraindication: Left atrial thrombus, moderate MR

Open Mitral Commissurotomy: If mild calcif + leaflet/chordal thickening

– restenosis in 50% pts in 8 yrs

Valve replacement: mod-sev calcif and sev scarred leaflets



MR

Etiology

Mitral valve prolapse

Congenital cleft leaflets, LV

dilatation/aneurysm (CHF, DCM, myocarditis), IE abscess, Marfan's

syndrome, HOCM, acute MI, myxoma, MV annulus calcification, chordae/papillary muscle trauma/ischemia/rupture, rheumatic disease

Pathophysiology

Reduced CO \rightarrow increased LV and LA pressure \rightarrow LV and LA dilatation \rightarrow CHF and pulmonary HTN

Symptoms

Dyspnea, PND, orthopnea, palpitations, peripheral edema

Physical Exam

Displaced, hyperdynamic apex, left parasternal lift, apical thrill

Auscultation: holosystolic murmur at apex, radiating to axilla \pm mid-diastolic rumble, loud S₂ (if pulmonary HTN), S₃

Investigations

ECG: LAE, left atrial delay (bifid P waves), \pm LVH

CXR: LVH, LAE, pulmonary venous HTN

Echo: severity of MR, LV function, leaflets

Swan-Ganz: prominent LA "v" wave

Treatment

Asymptomatic: serial Echos,

Symptomatic: decrease preload (diuretics), decrease afterload (ACEIs) for severe MR and poor surgical candidate; stabilize acute MR with vasodilators before surgery

Surgery if: acute MR with CHF, papillary muscle rupture, NYHA class III-IV CHF, AF, LVEF $<60\%$, increasing LV size, earlier surgery if valve repairable

Surgical Options

Valve repair: $>75\%$ of pts with MR and myxomatous MV disease (MVP)

– annuloplasty rings, leaflet repair, chordae transfers/shorten/replacement

Valve replacement: failure of repair, heavily calcified annulus

Advantage of repair: low rate of endocarditis, no anticoagulation, less chance of re-operation



Table 15. Valvular Heart Disease (continued)**TS****Etiology**

Rheumatic disease, congenital, carcinoid, fibroelastosis; usually accompanied by MS

Pathophysiology

Increased RA pressure → right heart failure → decreased CO and fixed on exertion

Symptoms

Peripheral edema, fatigue, palpitations

Physical Exam

Prominent “a” waves in JVP, +ve abdominojugular reflex, Kussmaul’s sign, diastolic rumble 4th left intercostal space

Investigations

ECG: RAE

CXR: dilatation of RA without pulmonary artery enlargement

Echo: diagnostic

Treatment

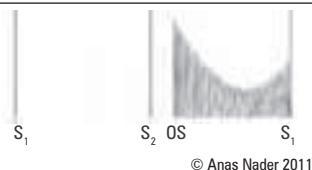
Preload reduction (diuretics)

Surgery if: usually only if other surgery needed (e.g. MVR)

Surgical Options

Valve Replacement:

- If severely diseased valve
- Bioprosthesis preferred

**TR****Etiology**

RV dilatation, IE (IV drug use), rheumatic disease, congenital (Ebstein anomaly), carcinoid

Pathophysiology

RV dilatation → TR → further RV dilatation → right heart failure

Symptoms

Peripheral edema, fatigue, palpitations

Physical Exam

“cv” waves in JVP, +ve abdominojugular reflex, Kussmaul’s sign, holosystolic murmur at LLSB accentuated by inspiration, left parasternal lift

Investigations

ECG: RAE, RVH, AF

CXR: RAE, RV enlargement

Echo: diagnostic

Treatment

Preload reduction (diuretics)

Surgery if: usually only if other surgery needed (e.g. MVR)

Surgical Options

Annuloplasty, i.e. repair (rarely replacement)

**PS****Etiology**

Usually congenital, rheumatic disease (rare), carcinoid

Pathophysiology

Increased RV pressure → RV hypertrophy → right heart failure

Symptoms

Chest pain, syncope, fatigue, peripheral edema

Physical Exam

Systolic murmur at 2nd LICS accentuated by inspiration, pulmonary ejection click, right-sided S4

Investigations

ECG: RVH

CXR: prominent pulmonary arteries enlarged RV

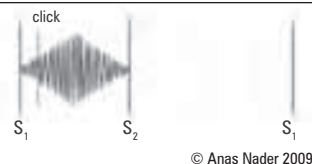
Echo: diagnostic

Treatment

Balloon valvuloplasty if severe symptoms

Surgical Options

Percutaneous or open balloon valvuloplasty

**PR****Etiology**

Pulmonary HTN, IE, rheumatic disease, tetralogy of Fallot (post-repair)

Pathophysiology

Increased RV volume → increased wall tension → RV hypertrophy → right heart failure

Symptoms

Chest pain, syncope, fatigue, peripheral edema

Physical Exam

Early diastolic murmur at LLSB, Graham Steell (diastolic) murmur 2nd and 3rd LICS increasing with inspiration

Investigations

ECG: RVH

CXR: prominent pulmonary arteries if pulmonary HTN; enlarged RV

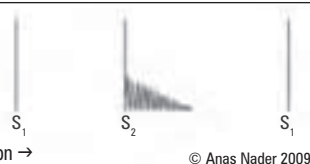
Echo: diagnostic

Treatment

Rarely requires treatment; valve replacement if severe

Surgical Options

Pulmonary valve replacement

**Mitral Valve Prolapse****Etiology**

Myxomatous degeneration of chordae; thick, bulky leaflets that crowd orifice; Marfan’s syndrome; pectus excavatum, straight back syndrome, other MSK abnormalities; <3% of population

Pathophysiology

MV displaced into LA during systole; no causal mechanisms found for symptoms

Symptoms

Prolonged, stabbing chest pain, dyspnea, anxiety/panic, palpitations, fatigue, presyncope

Physical Exam

Auscultation: mid-systolic click (billowing of mitral leaflet into LA; tensing of redundant valve tissue); mid to late systolic murmur at apex, accentuated by Valsalva or squat-to-stand maneuvers

Investigations

ECG: non-specific ST-T wave changes, paroxysmal SVT, ventricular ectopy

Echo: systolic displacement of thickened MV leaflets into LA

Treatment

Asymptomatic: no treatment; reassurance

Symptomatic: beta-blockers and avoidance of stimulants (caffeine) for significant palpitations, anticoagulation if systemic emboli

Surgical Options

Mitral valve surgery (repair favoured over replacement) if symptomatic and significant MR

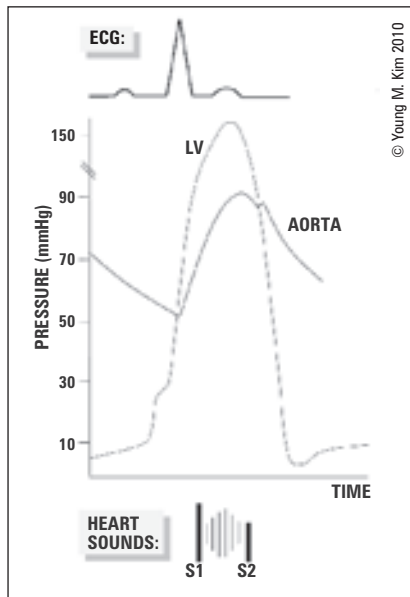


Figure 33. Hemodynamics of Aortic Stenosis

Stenosis across the aortic valve results in the generation of a significant pressure gradient between the left ventricle and the aorta and a crescendo-decrescendo murmur during systolic contraction. The stenosis decreases the intensity of aortic valve closure hence diminishing S2.

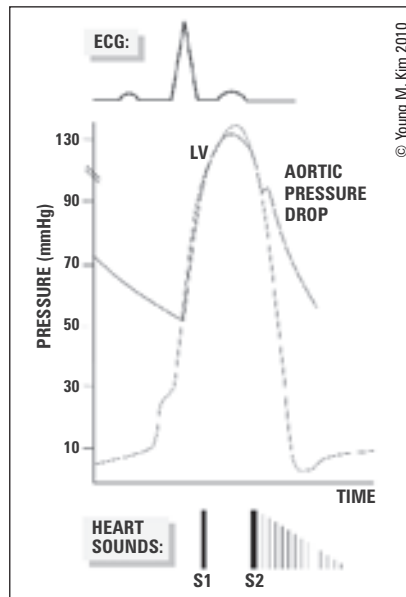


Figure 34. Hemodynamics of Aortic Regurgitation

Regurgitation across the aortic valve during diastole causes the aortic pressure to rapidly decrease and a decrescendo murmur can be heard at the onset of diastole (after S2 is audible). The presence of regurgitant blood from the aorta increases left-ventricular end-diastolic volume.

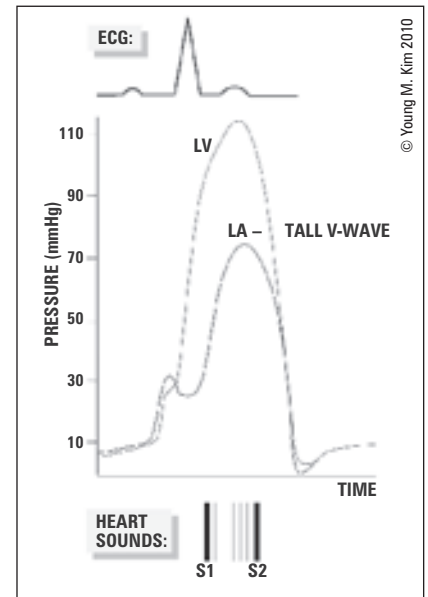


Figure 35. Hemodynamics of Acute Mitral Regurgitation

During systolic contraction, blood regurgitates from the left ventricle into the left atrium across the incompetent mitral valve resulting in an audible holosystolic murmur between S1 and S2. The portion of left ventricular end diastolic volume that regurgitates into the left atrial myocardium increases left atrial pressures resulting in a tall V-wave.

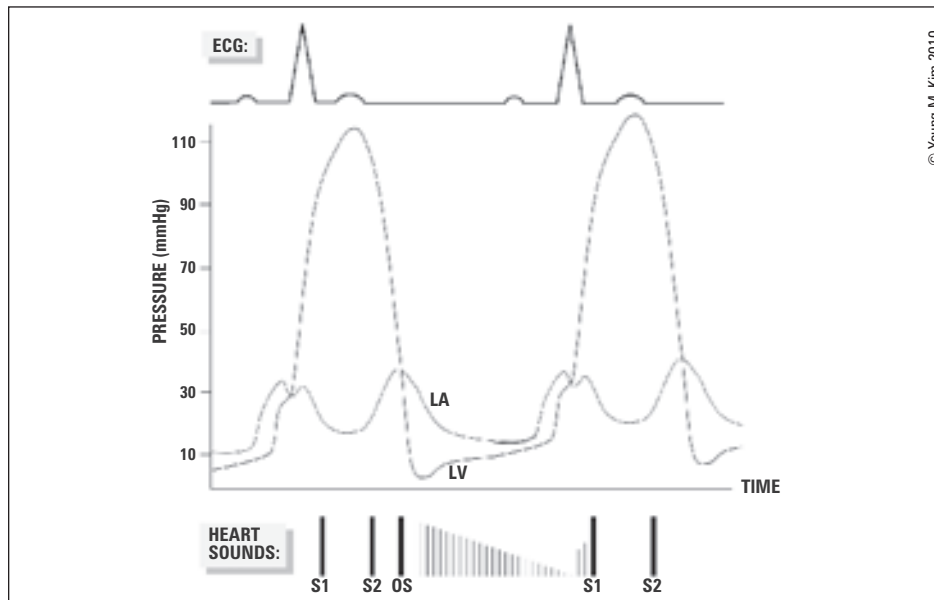


Figure 36. Hemodynamics of Mitral Stenosis

First note that the left atrial pressure exceeds the left ventricular pressure during diastole due to mitral stenosis and the consequent generation of a pressure gradient across the left atrium and left ventricle. In diastole, the stenotic mitral valve opens which corresponds to the opening snap (OS) and the passage of blood across the mitral stenosis results in an audible decrescendo murmur. Left atrial contraction prior to S1 increases the pressure gradient resulting in accentuation of the murmur before S1 is audible.

Pericardial Disease

Acute Pericarditis

Etiology of Pericarditis/Pericardial Effusion

- idiopathic is most common: usually presumed to be viral
- infectious
 - viral: Coxsackie virus A, B (most common), echovirus
 - bacterial: *S. pneumoniae*, *S. aureus*
 - TB
 - fungal: histoplasmosis, blastomycosis
- post-MI: acute (direct extension of myocardial inflammation, 1-7 days), Dressler's syndrome (autoimmune, 2-8 weeks)
- post-cardiac surgery (e.g. CABG), other trauma
- metabolic: uremia (common), hypothyroidism
- neoplasm: Hodgkin's, breast, lung, renal cell carcinoma, melanoma
- collagen vascular disease: SLE, polyarteritis, RA, scleroderma
- vascular: dissecting aneurysm
- other: drugs (e.g. hydralazine), radiation, infiltrative disease (sarcoid)

Signs and Symptoms

- diagnostic triad: chest pain, friction rub, and ECG changes
- pleuritic chest pain – alleviated by sitting up and leaning forward
- pericardial friction rub – may be uni-, bi- or triphasic
- \pm fever, malaise

Investigations

- ECG: initially diffuse elevated ST segments \pm depressed PR segment, the elevation in the ST segment is concave upwards \rightarrow 2-5 days later ST isoelectric with T wave flattening and inversion
- CXR: normal heart size, pulmonary infiltrates
- echo: assess pericardial effusion

Treatment

- treat the underlying disease
- anti-inflammatory agents (high dose NSAIDs/ASA, steroids if severe or recurrent); analgesics

Prognosis

- complications: recurrence, atrial arrhythmia, pericardial effusion, tamponade, constrictive pericarditis

Pericardial Effusion

Etiology

- transudative (serous)
 - CHF, hypoalbuminemia/hypoproteinemia, hypothyroidism
- exudative (serosanguinous or bloody)
 - causes similar to the causes of acute pericarditis
 - may develop acute effusion secondary to hemopericardium (trauma, post-MI myocardial rupture, aortic dissection)
- physiologic consequences depend on type and volume of effusion, rate of effusion development, and underlying cardiac disease

Signs and Symptoms

- may be asymptomatic or similar to acute pericarditis
- dyspnea, cough
- extra-cardiac (esophageal/recurrent laryngeal nerve/tracheo-bronchial/phrenic nerve irritation)
- JVP increased with dominant "x" descent
- arterial pulse normal to decreased volume, decreased pulse pressure
- auscultation: distant heart sounds \pm rub

Investigations

- ECG: low voltage, flat T waves
- CXR: cardiomegaly, rounded cardiac contour
- echo (procedure of choice): fluid in pericardial sac
- pericardiocentesis: definitive method of determining transudate vs. exudate, identify infectious agents, neoplastic involvement

Treatment

- mild: frequent observation with serial echocardiograms, treat underlying cause, anti-inflammatory agents for inflammation
- severe: may develop cardiac tamponade



Acute Pericarditis
Chest Pain
Friction Rub
ECG Changes



Ewart's Sign
Bronchial breathing and dullness to percussion at the lower angle of the left scapula in pericardial effusion due to effusion compressing left lower lobe of lung.

Cardiac Tamponade

Etiology

- major complication of rapidly accumulating pericardial effusion; cardiac tamponade is a clinical diagnosis
- any cause of pericarditis but especially trauma, malignancy, uremia, idiopathic, proximal aortic dissection with rupture

Pathophysiology

- high intra-pericardial pressure → decreased venous return → decreased diastolic ventricular filling → decreased CO → hypotension and venous congestion

Signs and Symptoms

- tachypnea, dyspnea, shock, muffled heart sounds
- pulsus paradoxus (inspiratory fall in systolic BP >10 mmHg during quiet breathing)
- JVP “x” descent only, absent “y” descent
- hepatic congestion/peripheral edema

Investigations

- ECG: electrical alternans (pathognomonic variation in R wave amplitude), low voltage
- echo: pericardial effusion, compression of cardiac chambers (RA and RV) in diastole
- cardiac catheterization

Treatment

- pericardiocentesis – echo- or ECG-guided
- pericardiectomy
- avoid diuretics and vasodilators (these decrease venous return to already under-filled RV → decrease LV preload → decrease CO)
- fluid administration i.e. saline load may temporarily increase CO
- treat underlying cause



Classic quartet of tamponade: hypotension, increased JVP, tachycardia, pulsus paradoxus.



Beck's Triad: hypotension, increased JVP, muffled heart sounds.



DDx Pulsus Paradoxus

- Constrictive pericarditis
- Severe obstructive pulmonary disease (e.g. asthma)
- Tension Pneumothorax
- Pulmonary embolus
- Cardiogenic shock

Constrictive Pericarditis

Etiology

- chronic pericarditis resulting in fibrosed, thickened, adherent, and/or calcified pericardium
- any cause of acute pericarditis may result in chronic pericarditis
- major causes are idiopathic, post-infectious (viral, TB), radiation, post-cardiac surgery, uremia, MI

Signs and Symptoms

- dyspnea, fatigue, palpitations
- abdominal pain
- may mimic CHF (especially right-sided HF)
 - ascites, hepatosplenomegaly, edema
- increased JVP, Kussmaul's sign (paradoxical increase in JVP with inspiration), Friedreich's sign (prominent “y” descent)
- BP usually normal (and usually no pulsus paradoxus)
- precordial examination: ± pericardial knock (early diastolic sound)
- see Table 16 for differentiation from cardiac tamponade

Investigations

- ECG: non-specific: low voltage, flat T wave, ± AF
- CXR: pericardial calcification, effusions
- echo/CT/MRI: pericardial thickening
- cardiac catheterization: equalization of end-diastolic chamber pressures (diagnostic)

Treatment

- medical: diuretics, salt restriction
- surgical: pericardiectomy (only if refractory to medical therapy)
- prognosis best with idiopathic or infectious cause and worst in post-radiation with death resulting from heart failure

Table 16. Differentiation of Constrictive Pericarditis vs. Cardiac Tamponade

Characteristic	Constrictive Pericarditis	Tamponade
JVP	“y” > “x”	“x” > “y”
Kussmaul's sign	Present	Absent
Pulsus paradoxus	Uncommon	Always
Pericardial knock	Present	Absent
Hypotension	Variable	Severe

VASCULAR DISEASE

Peripheral Arterial Disease

Acute Arterial Occlusion/Insufficiency

Definition

- acute occlusion/rupture of a peripheral artery
- urgent management required: >6 hours results in irreversible ischemia and myonecrosis
- lower extremity > upper extremity; femoropopliteal > aortoiliac

Etiology

- embolus
 - cardiac embolus (80-90%): history of MI <3 months, valvular disease, AF, cardiomyopathy, endocarditis, atrial myxoma
 - arterial embolus: proximal arterial aneurysm, atheroembolism
 - venous embolus (intracardiac shunt); may have Hx of OCP use
 - Hx of TIAs/strokes
- thrombus
 - atherosclerotic, congenital anomaly, infection, hematological disorders and stasis
- trauma
 - arterial catheterization, intra-arterial drug injection induced, aortic dissection, severe venous thrombophlebitis, prolonged immobilization
- idiopathic

Clinical Features

- general
 - pain in lower extremity progressing within hours to a feeling of cold, numbness, loss of function and sensation
 - symptoms (6 P's) – all may not be present
 - ♦ Pain: absent in 20% of cases due to prompt onset of anesthesia and paralysis
 - ♦ Pallor: within a few hours becomes mottled cyanosis
 - ♦ Paresthesia: light touch (small fibres) lost first then sensory modalities (large fibres)
 - ♦ Paralysis/Power loss: most important, heralds impending gangrene
 - ♦ Polar (cold)
 - ♦ Pulselessness: not reliable
- embolus vs. thrombus – dramatically different treatment (see Table 17)

Investigations

- CXR, ECG, arteriography

Treatment

- immediate heparinization with 5000 IU bolus and continuous infusion to maintain PTT >60 seconds
- absent power and sensation – emergent revascularization
- present power and sensation – work-up (including angiogram)
- definitive treatment
 - embolus: embolectomy
 - thrombus: thrombectomy ± graft, ± bypass
 - irreversible ischemia: amputation
- identify and treat underlying cause
- continue heparin post-op, start warfarin post-op day 1 for 3 months

Table 17. Differentiation of Arterial Embolism and Thrombosis

Presentation	Embolus	Thrombus
Onset	Acute	Progressive, acute-on-chronic
Loss of function/sensation	Prominent	Less profound
Hx of claudication	No	Yes
Atrophic changes	No	Yes
Contralateral limb pulses	Yes	Decreased or absent

Complications

- compartment syndrome with prolonged ischemia; requires fasciotomy
- renal failure and multi-organ failure due to toxic metabolites from ischemic muscle

Prognosis

- 12-15% mortality rate
- 5-40% morbidity rate (amputation)



Differential of Claudication

Vascular

- Atherosclerotic disease
- Vasculitis (e.g. Buerger's disease, Takayasu's arteritis)
- Diabetic neuropathy
- Venous disease (e.g. DVT, varicose veins)
- Popliteal entrapment syndrome

Neurologic

- Neurospinal disease (e.g. spinal stenosis)
- Reflex sympathetic dystrophy

MSK

- Osteoarthritis
- Rheumatoid arthritis/connective tissue disease
- Remote trauma

Chronic Arterial Occlusion/Insufficiency

Etiology

- predominantly due to atherosclerosis: primarily lower extremities with symptoms related to the location of obstruction

Risk Factors

- major: smoking, DM, hyperhomocysteinemia
- minor: HTN, hyperlipidemia, family history, obesity, sedentary lifestyle, male gender

Clinical Features

- claudication
 - pain with exertion: usually in calves or any exercising group
 - relieved by short rest: 2 to 5 minutes, and no postural changes necessary
 - reproducible: same distance to elicit pain, same location of pain, same amount of rest to relieve pain
- pulses may be absent at some locations, bruits may be present
- signs of poor perfusion: hair loss, hypertrophic nails, atrophic muscle, skin ulcerations and infections, slow capillary refill, prolonged pallor with elevation and rubor on dependency, venous troughing (collapse of superficial veins of foot)
- other manifestations of atherosclerosis: CVD, CAD, impotence, splanchnic ischemia



Signs of Peripheral Vascular Insufficiency

SICVD

Symmetry of leg musculature
Integrity of skin
Colour of toe nails
Varicose veins
Distribution of hair

Differential Diagnosis

- osteoarthritis (OA): worse at night and varies day-to-day
- neurogenic claudication: due to spinal stenosis or radiculopathy; pain very similar but relieved by longer rest and postural changes
- varicose veins: localized pain, typically less severe, after exercise and never at rest; related to the presence and site of varices
- inflammatory processes: Buerger's disease, Takayasu's arteritis
- other: popliteal entrapment (e.g. tumour, Baker's cyst), radiation injury, remote trauma

Investigations

- non-invasive
 - ankle-brachial index (ABI) (grade 1A recommendation): measure brachial and ankle pressures bilaterally (use highest value) generally, ABI <0.90 abnormal, rest pain appears at <0.3 (see Table 18)
 - CTA and MRA – excellent correlation with arteriography, where available, can replace it for intervention planning (grade 1A recommendation)
 - Doppler segmental pressures and pulse volume recordings, transcutaneous oxygen studies (photoplethysmography) treadmill exercise claudication test and real-time duplex scanning considered by vascular specialist (grade 3C)
- invasive
 - arteriography (gold standard): defines site and size of occlusion, and collateral flow status, operative planning tool

Table 18. Ankle-Brachial Indices and Degrees of Ischemia

ABI recording	Degree of Ischemia
>0.95	Normal/no ischemia
0.85 – 0.94	Mild
0.50 – 0.84	Moderate
0.26 – 0.49	Severe
<0.25	Consider limb salvage
>1.2	Suspect wall calcification (most common in diabetics)

Treatment (see Figure 37)

- conservative
 - risk factor modification (smoking cessation improves prognosis, treatment of HTN, hyperlipidemia and/or DM)
 - exercise program – develops collateral circulation, improves exercise tolerance
 - foot care (especially DM)
- pharmacotherapy
 - anti-platelet agents (ECASA, clopidogrel or more rarely ticlopidine)
 - cilostazol (cAMP-phosphodiesterase inhibitor with anti-platelet and vasodilatory effects)
 - pain relief: opiate analgesia (morphine sulphate), supplemented by NSAIDs; if opiate analgesia inadequate, possibility of lumbar sympathectomy

- surgical/interventional
 - indications: claudication interfering with lifestyle, rest pain, pre-gangrene, gangrene
 - surgical options: endovascular (stenting/angioplasty) or arterial bypass grafts
 - bypass graft sites: aortofemoral, axillofemoral, femoropopliteal, distal arterial
 - graft choices: in situ graft – reversed vein graft, synthetic – polytetrafluoroethylene graft (Gor-Tex®) or Dacron®
 - amputation: if not suitable for revascularization and persistent serious infections and/or gangrene

Prognosis

- conservative therapy: 60-80% improve, 20-30% stay the same, 5-10% deteriorate, 5% will require intervention within 5 years, <4% will require amputation

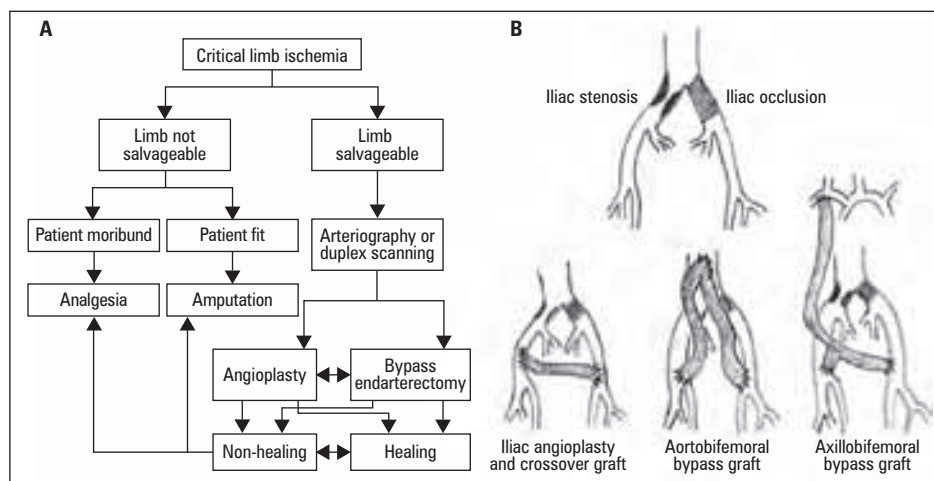


Figure 37. Treatment Options for Critical Limb Ischemia

(A) Algorithm for the treatment of critical limb ischemia

(B) Surgical treatment options for the treatment of aortoiliac disease

Modified from Beard JD. Chronic lower limb ischemia. *BMJ*. 2000; 320:854-857.

Hypertension

- see [Family Medicine](#), FM35

Pulmonary Hypertension

- see [Respirology](#), R16

Carotid Artery Disease

- see [Neurosurgery](#), NS21

Aortic Disease

Aortic Dissection

Definition

- tear in aortic intima allowing blood to dissect into the media; acute <2 weeks (initial mortality 1% per hour), chronic >2 weeks (mortality levels off to 75-80%)

Classification (see Figure 38)

- Stanford
 - Type A: involves ascending aorta ± aortic arch; requires emergency surgery
 - Type B: only involves aorta distal to subclavian artery; emergency surgery only if complications of dissection (requires long-term follow-up to assess aneurysm size)

- DeBakey
 - Type I: involves ascending and descending aorta, 50% of patients
 - Type II: ascending aorta only (stops at the innominate artery), 35% of patients
 - Type IIIA: descending thoracic aorta only (distal to left subclavian artery and proximal to diaphragm), 15% of patients (including Type IIIB)
 - Type IIIB: Type IIIA plus abdominal aorta

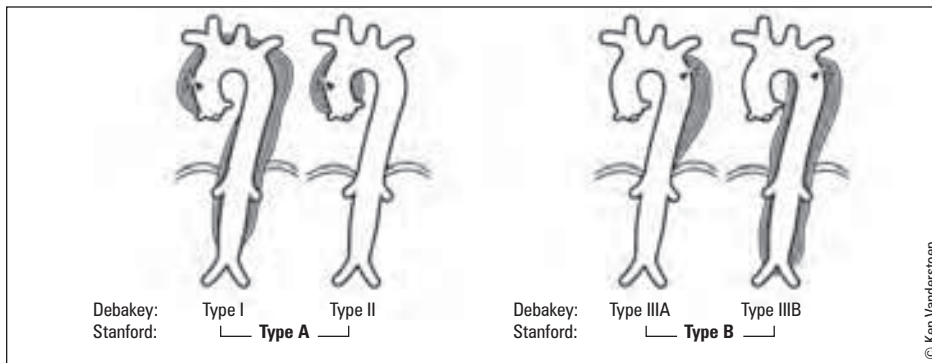


Figure 38. Classification of Aortic Dissection

Etiology

- most common: damage to aortic media (smooth muscle and elastic tissue), leading to degenerative/cystic changes due to hypertension
- other: cystic medial necrosis, atherosclerosis, connective tissue disease (Marfan's, Ehlers-Danlos), congenital conditions (coarctation of aorta, bicuspid aortic valves, patent ductus arteriosus), infection, trauma, arteritis (Takayasu's)

Epidemiology

- incidence of 5.2 in 1 000 000
- male:female = 3.2:1
- small increased incidence in African-Canadians (related to higher incidence of hypertension)
- lowest incidence in Asians
- peak incidence 50-65 yrs old; 20-40 yrs old with connective tissue diseases

Clinical Features

- sudden onset tearing chest pain that radiates to back with
 - hypertension (75-85% of patients)
 - asymmetric BPs and pulses between arms (>30 mmHg difference indicates poor prognosis)
 - ischemic syndromes due to occlusion of aortic branches: coronary (MI), carotids (ischemic stroke, Horner's syndrome), splanchnic (ischemic gut)
 - "unseating" of aortic valve cusps (new diastolic murmur in 20-30%)
 - rupture into pleura (dyspnea, hemoptysis) or peritoneum (hypotension, shock) or pericardium (cardiac tamponade)
 - renal insufficiency
 - lower limb ischemia (cold legs)
 - syncope

Investigations

- CXR
 - pleural cap (pleural effusion in lung apices)
 - widened mediastinum
 - left pleural effusion with extravasation of blood
- TEE: can visualize aortic valve and thoracic aorta but not abdominal aorta
- ECG: LVH, \pm MI, pericarditis, heart block
- CT, aortography, MRA: 100% sensitive and specific
- bloodwork: LDH (r/o ischemic gut), amylase (r/o pancreatitis), troponin (r/o MI)

Treatment

- pharmacologic
 - sodium nitroprusside and beta-blocker to lower BP and decrease cardiac contractility
 - beta-blocker given first to blunt reflex tachycardia and inotropy that will occur with sodium nitroprusside (vasodilator) then lower sBP with nitroprusside
 - target sBP of 110mmHg and HR of 60 bpm

- surgical
 - resection of intimal tear, reconstitution of flow through true lumen, replacement of the affected aorta with prosthetic graft, correction of any predisposing factors (e.g. bicuspid aortic valve, PDA, etc.)
 - post-operative complications: renal failure, intestinal ischemia, stroke, paraplegia, persistent leg ischemia, death
 - 2/3 of patients die of operative or post-operative complications
 - Type A: requires emergent surgery with cardiopulmonary bypass, may require hypothermic circulation for transverse arch dissections, valve replacement and coronary re-implantation for aortic root involvement, initial mortality rate without surgery is 3% per hour for first 24 hours, 30% 1 week, 80% 2 weeks
 - Type B: initially managed medically – 10-20% require urgent operation for complications (expansion, rupture, compromise of branch arteries, refractory HTN, or ongoing pain)
 - with treatment, 60% 5 yr survival, 40% 10 yr survival

Aortic Aneurysm

Definition of Aneurysm

- localized dilatation of an artery having a diameter at least 1.5 times that of the expected normal diameter of that given aortic segment
 - true aneurysm: involving all vessel wall layers (intima, media and adventitia)
 - false aneurysm: disruption of the aortic wall or the anastomotic site between vessel and graft with containment of blood by fibrous capsule made of surrounding tissue
- aneurysms can rupture, thrombose, embolize or erode and fistulize

Classification

- thoracic (TAA): ascending, transverse arch, descending
- thoracoabdominal
- abdominal (AAA): 90-98% are infrarenal

Etiology

- degenerative
- atherosclerotic
- traumatic
- mycotic (*Salmonella*, *Staphylococcus*, usually suprarenal)
- connective tissue disorder (Marfan syndrome, Ehlers-Danlos)
- vasculitis
- infectious (syphilis, fungal)
- ascending thoracic are associated with bicuspid aortic valve
- risk factors: smoking, HTN, age >70, family history

Epidemiology

- incidence 4.7 to 31.9 per 100 000 for AAA and 5.9 per 100 000 for TAA
- high risk groups
 - 65 years and older
 - male:female = 3.8:1
 - PVD, CAD, CVD
 - family history of AAA

Clinical Features

- common presentation: due to acute expansion or disruption of wall
 - syncope
 - pain (chest, abdominal, flank, back)
 - hypotension
 - palpable pulsatile mass above the umbilicus, pulsatile abdominal mass in two directions
 - airway or esophageal obstruction, hoarseness (left recurrent laryngeal nerve paralysis), hemoptysis, or hematemesis
 - distal pulses may be intact
- 75% asymptomatic (discovered incidentally)
- uncommon presentation
 - partial bowel obstruction
 - ureteric obstruction and hydronephrosis
 - GI bleed (duodenal mucosal hemorrhage, aortoduodenal fistula)
 - aortocaval fistula
 - distal embolization (blue toe)
- associated diseases
 - hypertension, PVD, CAD, COPD, renal insufficiency
- most commonly in the abdominal aorta (50% abdominal aorta, 40% thoracic aorta, 10% ascending aorta)



ACC/AHA 2005 Guidelines define an AAA when the minimum AP diameter of abdominal aorta ≥ 3.0 cm.



Classic Triad of Ruptured AAA

- Pain
- Hypotension
- Pulsatile abdominal mass



ACC/AHA 2005 Guidelines Suggest

1. Men ≥ 60 yrs with AAA in first-degree relative should have U/S screening for AAA.
2. Men 60-75 yrs who have ever smoked should have one-time U/S screening for AAA.

Investigations

- bloodwork: CBC, electrolytes, urea, creatinine, PTT, INR, type and cross
- abdominal U/S (100% sensitive, up to ± 0.6 cm accuracy in size determination)
- CT (accurate visualization, size determination)
- MRI (accurate visualization, limited access)
- aortogram
- Doppler/duplex (r/o vascular tree aneurysms elsewhere)

Treatment**Conservative**

- cardiovascular risk factor reduction: smoking cessation, HTN control, DM and hyperlipidemia control
- regular exercise
- watchful waiting, U/S every 6 months to 3 years depending on size and location

Surgical

- when risk of rupture greater than or equal to risk of surgery (>5.5 cm)
- risk of rupture depends on
 - size
 - rate of enlargement >0.4 cm/yr
 - symptoms, comorbidities (HTN, COPD, dissection), smoking
- elective AAA repair mortality 2-5%; elective TAA repair mortality $<10\%$ (highest with proximal aortic and thoracoabdominal repairs)
- consider revascularization for patients with CAD before elective repair of aneurysm
- indications
 - general: ruptured, symptomatic, mycotic, associated with acute Type A dissection or complicated Type B dissection or when risk of rupture is greater than risk of surgery (size >5.5 cm or $>2\times$ normal lumen size)
 - ascending thoracic aortic aneurysms
 - ♦ symptomatic, enlarging, diameter >5.5 cm or $>2\times$ normal lumen size, >4.5 cm and aortic regurgitation (annuloaortic ectasia); ≥ 5 cm in Marfan syndrome
- contraindications: life expectancy <1 year, terminal disease (e.g. cancer), significant co-morbidities (recent MI, unstable angina), decreased mental acuity, advanced age
- surgical options
 - open surgery (laparotomy) with graft replacement
 - ♦ possible complications
 - early: renal failure, spinal cord injury (paraparesis or paraplegia), impotence, arterial thrombosis, anastomotic rupture or bleeding, peripheral emboli
 - late: graft infection/thrombosis, aortoenteric fistula, anastomotic (pseudo) aneurysm
 - endoluminal graft placement under image guidance
 - ♦ newer procedure; high success rates in patients with suitable anatomy and experienced centres
 - ♦ advantages: decreased morbidity and mortality, procedure time, need for transfusion, ICU admissions, length of hospitalization, and recovery time
 - ♦ disadvantages: endoleak rates as high as 20-30%, device failure increasing as longer follow-up periods are achieved, re-intervention rates 10-30%, cost-effectiveness is an issue (devices are very expensive)
 - ♦ complications
 - early: immediate conversion to open repair, groin hematoma, arterial thrombosis, iliac artery rupture, and thromboemboli
 - late: endoleak, severe graft kinking, migration, thrombosis, rupture of aneurysm

**Management of Ruptured AAA**

- No imaging
- Straight to OR (confirm diagnosis by laparotomy)
- Crossmatch 10 units PRBCs
- Start IV if possible

**Risk of AAA Rupture**

Size	1-year rupture risk
<4 cm	0%
4-4.9 cm	1%
5-5.9 cm	5-10%
6-6.9 cm	10-20%
7-7.9 cm	20-40%

**Repair of Asymptomatic AAA is Generally Not Justified for:**

- Males <5.0 cm
- Females <4.5 cm

Peripheral Venous Disease

Deep Venous Thromboembolism

- see Hematology, H31

Superficial Thrombophlebitis

Definition

- erythema, induration, and tenderness along the superficial vein; usually spontaneous but can follow venous cannulation



Migratory superficial thrombophlebitis is often a sign of underlying malignancy ("Trousseau's disease").

Etiology

- infectious: suppurative phlebitis (complication of intravenous cannulation; associated with fever, chills)
- trauma
- inflammatory: varicose veins, migratory superficial thrombophlebitis, Buerger's disease, SLE
- hematologic: polycythemia, thrombocytosis
- neoplastic: occult malignancy (especially pancreatic)
- idiopathic

Clinical Features

- most common in greater saphenous vein and its tributaries
- pain and cord-like swelling along course of involved vein
- areas of induration, erythema and tenderness correspond to dilated and often thrombosed superficial veins
- complications
 - simultaneous DVT (up to 20% of cases), pulmonary embolus (rare unless DVT)
 - recurrent superficial thrombophlebitis

Investigations

- non-invasive tests (e.g. Doppler ultrasonography) to exclude associated DVT

Treatment

- conservative
 - bedrest and elevation of limb
 - moist heat, compression bandages, mild analgesic, anti-inflammatory and anti-platelet (e.g. ASA), ambulation
- surgical excision of involved vein
 - indication: failure of conservative measures (symptoms that persist over 2 weeks)
 - suppurative thrombophlebitis: broad-spectrum IV antibiotics and excision

Varicose Veins

Definition

- distention of tortuous superficial veins resulting from incompetent valves in the deep, superficial, or perforator systems
- distribution: greater saphenous vein and tributaries (most common), esophagus, anorectum, scrotum

Etiology

- primary
 - main factor: inherited structural weakness of valves
 - contributing factors: increasing age, female gender, OCP use, occupations requiring long hours of standing, pregnancy, obesity
- secondary
 - malignant pelvic tumours with venous compression
 - congenital anomalies – arteriovenous fistulae

Epidemiology

- most common form of venous disorder of lower extremity
- 10-20% of population

Clinical Features

- diffuse aching, fullness/tightness, nocturnal cramping
- aggravated by prolonged standing (end of day), premenstrual
- visible long, dilated and tortuous superficial veins along thigh and leg
- ulceration, hyperpigmentation, and induration (secondary varicosities)
- associated esophageal varices (GI bleed), hemorrhoids, varicocele
- Brodie-Trendelenberg test (valvular competence test)
 - with patient supine, raise leg and compress saphenous vein at thigh; have patient stand; if veins fill quickly from top down then incompetent valves; use multiple tourniquets to localize incompetent veins

Complications

- recurrent superficial thrombophlebitis
- hemorrhage: external or subcutaneous
- ulceration, eczema, lipodermatosclerosis, and hyperpigmentation

Treatment

- largely a cosmetic problem
- conservative: elevation of leg and/or elastic stockings
- surgical: high ligation and stripping of the long saphenous vein and its tributaries, sclerotherapy, endovenous laser therapy (EVLT)

Prognosis

- natural history benign, slow with predictable complications
- almost 100% symptomatic relief with treatment if varicosities are primary
- good cosmetic results with treatment
- significant post-operative recurrence, especially with sclerosing agent injection

Chronic Venous Insufficiency

Definition

- chronic elevation of deep venous pressure and blood pooling in lower extremities

Etiology

- calf muscle pump dysfunction and valvular incompetence (valvular reflux) due to phlebitis, varicosities, or DVT
- venous obstruction
- AV fistulas, venous malformations

Clinical Features

- pain (most common), ankle and calf edema – relieved by foot elevation
- pruritis, brownish hyperpigmentation (hemosiderin deposits)
- stasis dermatitis
- ulceration: shallow, above medial malleolus, weeping (wet), painless, irregular outline
- signs of DVT/varicose veins/thrombophlebitis

Investigations

- ambulatory venous pressure measurement (gold standard)
- Doppler U/S (most commonly used)
- photoplethysmography

Treatment

- conservative
 - elastic compression stockings, leg elevation, avoid prolonged sitting/standing
 - ulcers: zinc-oxide wraps, split-thickness skin grafts, antibiotics, debridement
- surgical
 - if conservative measures fail, or if recurrent/large ulcers
 - surgical ligation of perforators in region of ulcer, greater saphenous vein stripping
 - venous bypass if short segment obstruction

Lymphedema

Definition

- obstruction of lymphatic drainage resulting in edema with high protein content

Etiology

- primary: Milroy's syndrome
- secondary
 - infection: filariasis (#1 cause worldwide), post-operative
 - malignant infiltration: axillary, groin or intrapelvic
 - radiation/surgery (axillary, groin lymph node removal): #1 cause in North America

Clinical Features

- classically non-pitting edema
- impaired limb mobility; discomfort/pain; psychological distress

Treatment

- avoid limb injury (can precipitate or worsen lymphedema)
- skin hygiene
 - daily skin care with moisturizers
 - topical treatment of fungal infection; systemic treatment of bacterial infection
- external support
 - intensive: compression bandages
 - maintenance: lymphedema sleeve
- exercise
 - gentle daily exercise of affected limb, gradually increasing ROM
 - must wear a sleeve/bandages when doing exercises
- massage and manual lymph drainage therapy

Prognosis

- if left untreated, becomes resistant to treatment due to subcutaneous fibrosis
- cellulitis causes rapid increase in swelling: can lead to sepsis and death



Pitting edema → vascular
Non-pitting edema → lymphatic

Common Medications

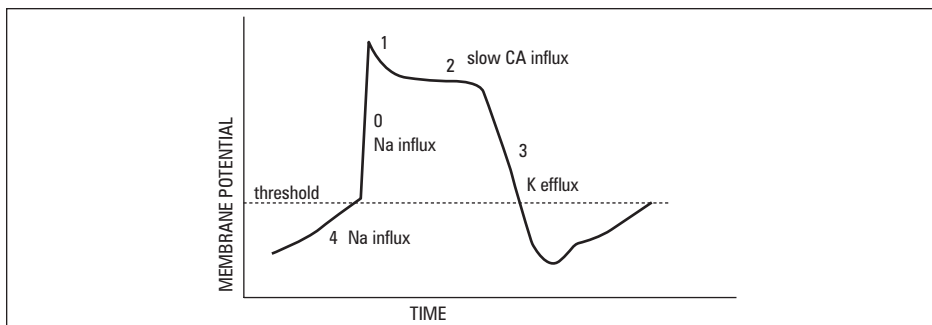
Table 19. Commonly Used Cardiac Therapeutics

Drug Class	Examples	Mechanism of Action	Indications	Side Effects	Contraindications
ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEIS)					
	enalapril (Vasotec®), perindopril (Coversyl®), ramipril (Altace®) lisinopril	Inhibit ACE-mediated conversion of angiotensin I to angiotensin II (AT II), causing peripheral vasodilation and decreased aldosterone synthesis	HTN, CAD, CHF, post-MI, DM	Dry cough, 10% hypotension, fatigue, hyperkalemia, renal insufficiency, angioedema	Bilateral renal artery stenosis, pregnancy, caution in decreased GFR
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)					
	candesartan, irbesartan, valsartan	Block AT II receptors, causing similar effects to ACEIs	Same as ACEIs, although evidence is generally less for ARBs. Often used when ACEIs are not tolerated.	Similar to ACEIs, but do not cause dry cough	Same as ACEIs
β-BLOCKERS					
β ₁ antagonists	atenolol, metoprolol, bisoprolol	Block β-adrenergic receptors, decreasing HR, BP, contractility, and myocardial oxygen demand, slow conduction through the AV node	HTN, CAD, acute MI, post-MI, CHF (start low and go slow), AF, SVT	Hypotension, fatigue, light- headedness, depression, bradycardia, hyperkalemia, bronchospasm, impotence, depression of counterregulatory response to hypoglycemia, exacerbation of Raynaud's phenomenon and claudication	Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, WPW. Caution in asthma, claudication, Raynaud's phenomenon, and decompensated CHF
β ₁ /β ₂ antagonists	propranolol				
α ₁ /β ₁ /β ₂ antagonists	labetalol, carvedilol				
β ₁ antagonists with ISA	acebutalol				
CALCIUM CHANNEL BLOCKERS (CCBS)					
Benzothiazepines Phenylalkylamines (non-dihydropyridines)	diltiazem verapamil	Block smooth muscle and myocardial calcium channels causing effects similar to β-blockers Also vasodilate	HTN, CAD, SVT, diastolic dysfunction	Hypotension, bradycardia, edema Negative inotrope	Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, WPW, CHF
Dihydropyridines	amlodipine (Norvasc®), nifedipine (Adalat®), felodipine (Plendil®)	Block smooth muscle calcium channels causing peripheral vasodilation	HTN	Hypotension, edema, flushing, headache, light-headedness	Severe aortic stenosis and liver failure
DIURETICS					
Thiazides	hydrochlorothiazide, chlorthalidone metolazone	Reduce Na reabsorption in the DCT	HTN (drugs of choice for uncomplicated HTN)	Hypotension, hypokalemia, polyuria	Sulfa allergy, pregnancy
Loop diuretics	furosemide (Lasix®)	Blocks Na/K-ATPase in the loop of Henle	CHF, pulmonary or peripheral edema	Hypovolemia, hypokalemic metabolic alkalosis	Hypovolemia, hypokalemia
Aldosterone receptor antagonists	spironolactone, eplerenone	Antagonize aldosterone receptors	HTN, CHF, hypokalemia	Edema, hyperkalemia, gynecomastia	Renal insufficiency, hyperkalemia, pregnancy
INOTROPES					
	digoxin (Lanoxin®)	Inhibit Na/K-ATPase, leading to increased intracellular Na and Ca concentration and increased myocardial contractility. Also slows conduction through the AV node	CHF, AF	AV block, tachyarrhythmias, bradyarrhythmias, blurred or yellow vision (van Gogh syndrome), anorexia, nausea and vomiting	2nd or 3rd degree AV block, hypokalemia, WPW
ANTICOAGULANTS					
Coumarins	warfarin (Coumadin®)	Antagonizes vitamin K, leading to decreased synthesis of clotting factors II, VII, IX, and X	Atrial fibrillation, LV dysfunction, prosthetic valves	Bleeding (by far the most important side effect), paradoxical thrombosis, skin necrosis	Recent surgery or bleeding, bleeding diathesis, pregnancy
Heparins	unfractionated heparin low molecular weight heparins (LMWHs): dalteparin, enoxaparin, tinzaparin	Antithrombin III agonist, leading to decreased clotting factor activity	Acute MI; when immediate anticoagulant effect needed	Bleeding, osteoporosis, heparin- induced thrombocytopenia (less in LMWHs)	Recent surgery or bleeding, bleeding diathesis, thrombocytopenia, renal insufficiency (for LMWHs)

Table 19. Commonly Used Cardiac Therapeutics (continued)

Drug Class	Examples	Mechanism of Action	Indications	Side Effects	Contraindications
ANTIPLATELETS					
Salicylates	ASA (Aspirin®)	Irreversibly acetylates platelet COX-1, preventing thromboxane A ₂ -mediated platelet aggregation	CAD, acute MI, post-MI, post-PCI and CABG	Bleeding, GI upset, gastrointestinal ulceration, impaired renal perfusion	Active bleeding or peptic ulcer disease (PUD)
Thienopyridines	clopidogrel (Plavix®), ticlopidine (Ticlid®)	Block platelet ADP receptors	Acute MI, post-MI, post-PCI and CABG	Bleeding, thrombotic thrombocytopenic purpura, neutropenia (ticlopidine)	Active bleeding or PUD
GPIIb/IIIa inhibitors	eptifibatide, tirofiban, abciximab	Block binding of fibrinogen to Gp IIb/IIIa	Acute MI, particularly if PCI is planned	Bleeding	Recent surgery or bleeding, bleeding diathesis
THROMBOLYTICS	alteplase, reteplase, tenecteplase, streptokinase	Convert circulating plasminogen to plasmin, which lyses cross-linked fibrin	Acute STEMI	Bleeding	See Table 7, C27
NITRATES	nitroglycerin	Relax vascular smooth muscle, producing venous and arteriolar dilation	CAD, MI, CHF (isosorbide dinitrate plus hydralazine)	Headache, dizziness, weakness, postural hypotension	Concurrent use of cGMP phosphodiesterase inhibitors, angle closure glaucoma, increased ICP
LIPID LOWERING AGENTS					
Statins	atorvastatin (Lipitor®), pravastatin (Pravachol®), rosuvastatin (Crestor®), simvastatin (Zocor®), lovastatin (Meracor®)	Inhibit hydroxymethylglutaryl CoA reductase, which catalyzes the rate-limiting step in cholesterol synthesis	Dyslipidemia (1° prevention of CAD), CAD, post-MI	Myalgia, rhabdomyolysis, abdominal pain	Liver or muscle disease

Antiarrhythmics

**Figure 39. Representative Action Potential****Table 20. Antiarrhythmic* Drugs (Vaughn-Williams Classification)**

Class	Agent	Indications	Side Effects	Mechanism of Action
Ia	quinidine, procainamide, disopyramide	SVT, VT	Torsades de Pointes (all Ia), diarrhea, Lupus-like syndrome, Anti-cholinergic effects	Moderate Na channel blockade Slows phase 0 upstroke Prolongs repolarization, slowing conduction
Ib	lidocaine, mexiletine	VT	Confusion, stupor, seizures, GI upset, tremor	Mild Na channel blockade Shortens phase 3 repolarization
Ic	propafenone, flecainide, encainide	SVT, VT, AF	Exacerbation of VT (all Ic), Negative inotropy (all Ic), Bradycardia and heart block (all Ic)	Marked Na channel blockade Markedly slows phase 0 upstroke
II	propranolol, metoprolol, etc.	SVT, AF	Bronchospasm, negative inotropy, bradycardia, AV block, impotence, fatigue	Beta-blocker Decreases phase 4 depolarization
III	amiodarone**, sotalol	SVT, VT, AF, SVT, VT, AF	Photosensitivity, pulmonary toxicity, hepatotoxicity, thyroid disease, increased INR, Torsades de Pointes, bradycardia, heart block and beta-blocker side effects	Blocks K channel Prolongs phase 3 repolarization, which prolongs refractory period
IV	verapamil, diltiazem	SVT, AF	Bradycardia, AV block, Hypotension	CCB Slows phase 4 spontaneous depolarization, slowing AV node conduction

*All antiarrhythmics have potential to be proarrhythmic

**Amiodarone has class I, II, III, and IV properties



Anti-Arrhythmic Drug Classification:
 Some Block Potassium Channels
 I – Sodium CB
 II – β -Blocker
 III – Potassium CB
 IV – CCB

Table 21. Actions of Alpha and Beta Adrenergic Receptors

Target System	ALPHA RECEPTORS		BETA RECEPTORS	
	Alpha1	Alpha2	Beta1	Beta2
Cardiovascular	<ul style="list-style-type: none"> Constriction of vascular smooth muscle Constriction of skin, skeletal muscle and splanchnic vessels Increased myocardial contractility Decreased heart rate 	<ul style="list-style-type: none"> Peripherally act to modulate vessel tone Vasoconstrict and dilate; oppose Alpha 1 vasoconstrictor activity 	<ul style="list-style-type: none"> Increased myocardial contractility Accelerate SA node Accelerate ectopic pacemakers 	<ul style="list-style-type: none"> Decreased vascular smooth muscle tone
Respiratory				<ul style="list-style-type: none"> Bronchodilation
Dermal	<ul style="list-style-type: none"> Pilomotor smooth muscle contraction Apocrine constriction 			
Ocular	<ul style="list-style-type: none"> Radial muscle contraction 		<ul style="list-style-type: none"> Ciliary muscle relaxation 	
Gastrointestinal	<ul style="list-style-type: none"> Inhibition of myenteric plexus Anal sphincter contraction 			
Genitourinary	<ul style="list-style-type: none"> Pregnant uterine contraction Penile and seminal vesicle ejaculation Urinary bladder contraction 	<ul style="list-style-type: none"> Smooth muscle wall relaxation 	<ul style="list-style-type: none"> Stimulation of renal renin release 	<ul style="list-style-type: none"> Bladder wall relaxation Uterine relaxation
Metabolic	<ul style="list-style-type: none"> Stimulate gluconeogenesis and glycogenolysis at the liver 	<ul style="list-style-type: none"> Fat cell lipolysis 	<ul style="list-style-type: none"> Fat cell lipolysis Glycogenolysis 	<ul style="list-style-type: none"> Gluconeogenesis

Adapted from the Family Practice Notebook (www.fpnotebook.com/NEU194.htm)

Table 22. Commonly Used Drugs that Act on Alpha and Beta Adrenergic Receptors

Mechanism of Action	ALPHA RECEPTORS			BETA RECEPTORS		
	Alpha1	Alpha1 and Alpha2	Alpha2	Beta1	Beta1 and Beta2	Beta2
Agonist	Phenylephrine Methoxamine	Epinephrine Norepinephrine	Clonidine	Norepinephrine Dobutamine	Isoproterenol Epinephrine	Albuterol Terbutaline
Antagonist	Prazosin Phenoxylbenzamine	Phentolamine	Yohimbine	Metoprolol Acebutolol Alprenolol Atenolol Esmolol	Propranolol Timolol Nadolol Pindolol Carvedilol	Butoxamine

Adapted from the Family Practice Notebook (<http://www.fpnotebook.com/NEU194.htm>)

Landmark Cardiac Trials

Trial	Reference	Results
ISCHEMIC HEART DISEASE		
4S	<i>Lancet</i> 1994; 344:1383-89	In patients with angina or previous MI and high total cholesterol, simvastatin reduced: all-cause mortality, fatal and nonfatal coronary events, need for coronary artery bypass surgery or angioplasty
A to Z: Phase Z	<i>JAMA</i> 2004; 292:1307-16	Early initiation of aggressive simvastatin regimen resulted in a trend towards reduced major cardiovascular events
ALLHAT	<i>JAMA</i> 2002; 288:2981-97	In hypertensive patients with ≥ 1 risk factors for CHD, neither amlodipine nor lisinopril reduced fatal CHD and nonfatal MI or all-cause mortality when compared with chlorthalidone (thiazide diuretics)
ASCOT-LLA	<i>Lancet</i> 2003; 361:1149-58	In hypertensive patients with risk factors for CHD and average or below-average cholesterol, atorvastatin reduced nonfatal MI, fatal CHD, fatal/nonfatal stroke, coronary events but not all-cause mortality
BHAT	<i>JAMA</i> 1982; 247:1707-14	In acute MI, propranolol reduced all-cause mortality, cardiovascular death and sudden death from atherosclerotic heart disease
CAPRIE	<i>Lancet</i> 1996; 348:1329-39	In atherosclerotic vascular disease, clopidogrel reduced the primary combined endpoint of stroke, MI or vascular death and improved peripheral arterial disease compared to aspirin
CARE	<i>NEJM</i> 1996; 335:1001-9	Pravastatin reduced MI and stroke in patients with previous MI and average cholesterol
COURAGE	<i>NEJM</i> 2008; 358:1887-98	Compared with optimal medical therapy alone, PCI + medical therapy did not reduce all-cause mortality and non-fatal MI, and it did not reduce the incidence of major cardiovascular events
CURE	<i>NEJM</i> 2001; 345:494-502	Clopidogrel plus aspirin reduced death from CV causes, non-fatal MI, or stroke but increased bleeding complications
EUROPA	<i>Lancet</i> 2003; 362:782-88	With stable CAD and no CHF, perindopril reduced cardiovascular death, MI and total mortality
FRISC II	<i>Lancet</i> 1999; 354:701-7	Dalteparin lowers risk of death, MI and the need for revascularization during the first month. These benefits are not sustained during longer term follow up
FRISC II	<i>Lancet</i> 1999; 354:708-15	Benefit of early invasive treatment in reduction of death or MI significant at 6 months
GISSI-3	<i>Lancet</i> 1994; 343:1115-22	In acute MI (<24 hours), lisinopril reduced mortality and severe ventricular dysfunction. Nitrate conferred no benefit except when combined with lisinopril
GUSTO-I	<i>NEJM</i> 1993; 329:673-82	Although there was an excess of hemorrhagic stroke with t-PA plus heparin, compared with the other regimens, the combined 30-day endpoint of death or disabling stroke was significantly lower with accelerated t-PA
HOPE	<i>NEJM</i> 2000; 342:154-60	In high-risk patients without low LVEF or CHF, ramipril reduced rates of death, MI, stroke, revascularization, new diagnosis of diabetes and complications due to diabetes. Vitamin E had no effect on outcomes.
HPS	<i>Lancet</i> 2002; 360:7-22	In high-risk patients with various cholesterol values, simvastatin reduced all-cause mortality, coronary deaths and major vascular events
ISIS-2	<i>Lancet</i> 1988; 2:349-60	Early therapy with SK and ASA in patients with MI individually and in combination significantly reduced all-cause mortality and in combination demonstrated additive effect
ISIS-4	<i>Lancet</i> 1995; 345:669-85	In patients with suspected or definite acute MI, early treatment with captopril reduced all-cause mortality at 35 days and during long-term follow up
LIPID	<i>NEJM</i> 1998; 339:1349-57	Pravastatin reduced both mortality due to CHD and overall mortality and had benefit for patients with unstable angina
OASIS-5	<i>NEJM</i> 2006; 354:1464-76	Compared to enoxaparin, fondaparinux reduced mortality rates, major bleeds at 9 and MI at 30d and 180d
OPTIMAAL	<i>Lancet</i> 2002; 360:752-60	Losartan 50 mg daily conferred no benefit in comparison with captopril
PROVE IT – TIMI 22	<i>NEJM</i> 2004; 350:1495-1504	In patients hospitalized for ACS, high-dose atorvastatin reduced all-cause mortality, MI, unstable angina, revascularization and stroke compared with pravastatin
SYNTAX	<i>NEJM</i> 2008; 360:961-972	CABG has lower rate of major cardiac or cerebrovascular events. The rate of stroke was increased with CABG, whereas the rate of repeat revascularization was increased with PCI
TNT	<i>NEJM</i> 2005; 352:1425-35	Lipid-lowering therapy with atorvastatin 80 mg/day in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/day
WOSCOPS	<i>NEJM</i> 1995; 333:1301-7	Pravastatin reduced nonfatal MI or death from CHD and need for myocardial revascularization procedures in patients with hypercholesterolemia and no MI

Trial	Reference	Results
HEART FAILURE		
AIRE	<i>Lancet</i> 1993; 342:821-8	Ramipril commenced 3-10 days after MI and continued for a mean 15-month period significantly reduced all-cause mortality in patients with non-severe CHF
CHARM	<i>Lancet</i> 2003; 362:759-66	Candesartan reduced overall mortality, cardiovascular death and CHF hospitalizations
CIBIS II	<i>Lancet</i> 1999; 353:9-13	Bisoprolol reduced all-cause mortality, cardiovascular death, all-cause hospitalization and CHF hospitalization
COMET	<i>Lancet</i> 2003; 362:7-13	Carvedilol was associated with a reduction in all cause mortality compared with metoprolol
CONSENSUS	<i>NEJM</i> 1987; 316:1429-35	Enalapril reduced all-cause mortality, death due to progression of heart failure
COPERNICUS	<i>NEJM</i> 2001; 344:1651-8	Carvedilol in addition to standard treatment significantly reduced the risk of death or hospitalization in patients with severe CHF
I-PRESERVE	<i>NEJM</i> 2008; 359:2456-2467	In patients with CHF and normal LVEF, treatment with ARB (irbesartan) did not improve mortality or cardiovascular morbidity compared to placebo
MERIT-HF	<i>Lancet</i> 1999; 353:2001-7	Metoprolol CR/XL daily in addition to optimum standard therapy improved survival in clinically stable patients, equating to prevention of 1 death per 27 patients treated per year
RALES	<i>NEJM</i> 1999; 341:709-17	In severe CHF and LVEF <35%, spironolactone reduced all-cause mortality, sudden death and death due to progression of heart failure
SAVE	<i>NEJM</i> 1992; 327:669-77	Patients with LV dysfunction post-MI, long-term captopril over 3.5y reduced the risk of death due to cardiovascular causes, recurrent MI, development of severe CHF and CHF hospitalization
SCD-HeFT	<i>NEJM</i> 2005; 352:225-237	In mild-to-moderate CHF, shock-only ICD significantly reduces risk of death. Amiodarone had no benefit compared with placebo in treating patients with mild-to-moderate CHF
SOLVD	<i>NEJM</i> 1991; 325:293-302	In stable chronic CHF with decreased LVEF (<0.35), long-term enalapril reduced death due to all causes and death or hospitalization due to CHF
TRACE	<i>NEJM</i> 1995; 333:1670-6	In patients with LV dysfunction post-MI, long-term trandolapril reduced the risk of death or progression to severe CHF and reduced risk of sudden death
V-HeFT II	<i>NEJM</i> 1991; 325:303-10	In chronic CHF, enalapril reduced mortality more than hydralazine-isosorbide for at least 2y. Treatment with either enalapril or hydralazine-isosorbide increased LVEF
DIABETES		
CARDS	<i>Lancet</i> 2004; 264:685-96	Atorvastatin reduces the risk of cardiovascular events in patients with type 2 diabetes
ONTARGET	<i>NEJM</i> 2008; 358:1547-59	In patients with vascular disease or diabetes without CHF, telmisartan is equally as effective as ramipril, with telmisartan causing a reduced risk of cough and angioedema, and an increased risk of hypotensive symptoms. Combination therapy offers no advantage
ARRHYTHMIA		
AFFIRM	<i>NEJM</i> 2002; 347:1825-33	No significant difference in mortality rates between rate or rhythm control
CAST	<i>NEJM</i> 1989; 321:406-12	Encainide or flecainide started ~15d after MI caused excessive mortality risk, excessive risk of death from arrhythmia in asymptomatic or mildly symptomatic ventricular arrhythmias after MI
HYPERTENSION		
HYVET	<i>NEJM</i> 2008; 358:1887-98	In hypertensive patients >80 y, treatment with indapamide, with or without perindopril, showed a trend towards reduced relative risk of fatal or non-fatal stroke
UKHDS (UKPDS)	<i>BMJ</i> 1998; 317:703-13	Hypertensive patients with DM and tight BP control at <150/85 mmHg by use of ACEi or beta-blocker reduced risk of diabetic complications and death related to diabetes and reduced risk of end-organ damage
VALUE	<i>Lancet</i> 2004; 363:2022-2031	Valsartan group had higher incidence of MI than amlodipine group, whereas amlodipine had a higher incidence of new onset diabetes
MISCELLANEOUS		
JUPITER	<i>NEJM</i> 2008; 359:2195-2207	With low to normal LDL-C and elevated hsCRP, treatment with rosuvastatin significantly reduced major cardiovascular events. NNT with rosuvastatin for 2 years to prevent one primary endpoint = 95
WHI	<i>JAMA</i> 2002; 288:321-333	Estrogen plus progestin therapy is associated with increased risks of cardiovascular disease and breast cancer but decreased risks of hip fracture and colorectal cancer in postmenopausal women

References

Ischemic Heart Disease

- Cannon CP, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *NEJM* 2004;350(15):1495-504.
- Lindahl, B., et al. Markers of Myocardial Damage and Inflammation in Relation to Long-Term Mortality in Unstable Coronary Artery Disease. *New England Journal of Medicine*. 2000; 343:1139-1147.
- Pitt B., et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *NEJM* 2003; 348(14):1309-21.
- Rauch, U., et al. Thrombus Formation on the Atherosclerotic Plaques: Pathogenesis and Clinical Consequences. *Annals of Internal Medicine*. 2001; 134: 224-238.
- The Arterial Revascularization Therapies Study Group. Comparison of Coronary-Artery Bypass Surgery and Stenting for the Treatment of Multivessel Disease. *New England Journal of Medicine*. 2001; 344:1117-1124.
- Turpie, A. G. G. and Antman, E. M. Low-Molecular-Weight Heparins in the Treatment of Acute Coronary Syndromes. *Archives of Internal Medicine*. 2001; 161: 1484-1490.
- Yeghiazarians, Y., Braunstein, J. B., Askari, A., and Stone, P. H. Review Article: Unstable Angina Pectoris. *New England Journal of Medicine*. 2000; 342:101-114.

Nuclear Cardiology

- Lee TH and Boucher CA. Noninvasive tests in patients with stable coronary artery disease (Review). *NEJM* 2000;344:1840-5.

Cardiomyopathies

- Feldman AM and McNamara D. Myocarditis (Review). *NEJM* 2000; 343:1388-98.

Guidelines

- ACC/AHA guidelines for percutaneous coronary intervention. *Circulation*. 2001;103:3019-3041.
- ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. (Available at: <http://www.acc.org>)
- ACC/AHA 2009 Focused Update on the Guidelines for the Diagnosis and Management of Heart Failure in Adults. *Circulation* 2009; 119:1977-2016.
- ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004; 110(9):e82-292.
- Antman EM et al. ACC/AHA Guidelines for the Management of Patients with ST-elevation Myocardial Infarction - summary: A Report of the American College of Cardiology. American Heart Association Task Force on Practice Guidelines. *Circulation*. 2004; 110-588.
- CCS. 2001 Canadian cardiovascular society consensus guideline update for the management and prevention of heart failure. *Canadian Journal of Cardiology*. 2001;17(supplE):5-24.
- Aurigemma, GP et al. Clinical Practice, Diastolic Heart Failure. *NEJM* 2004; 351:1097.
- www.acc.org – The American College of Cardiology (clinical guidelines, etc).
- www.ccs.ca – Canadian Cardiovascular Society 2005 Consensus Conference Peripheral Arterial Disease (Draft).
- www.theheart.org – Cardiology Online (requires registration).
- www.heartvalverepair.net – Heart Valve Repair Online.
- Beard JD. Chronic lower limb ischemia. *BMJ*. 2000;320:854-857.
- Fuchs JA. Atherogenesis and the Medical Management of Atherosclerosis. In *Vascular Surgery* 4th edition, Robert B. Rutherford Ed. 1995. WB. Saunders Co., Toronto. pp 222-234.
- Harrington RA et al. Antithrombotic Therapy for Coronary Artery Disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004; 126 (3 suppl):513s-584s.
- May J, White GH, and Harris JP. The complications and downside of endovascular therapies. *Adv Surg* 35: 153-72, 2001.
- Schmieder FA and Comerota AJ. Intermittent claudication: magnitude of the problem, patient evaluation, and therapeutic strategies. *Am J Card* 87 (Suppl): 3D-13D, 2001.
- Way LW, Doherty GM, editors. *Current Surgical Diagnosis and Treatment*, 11th edition. Lange Medical Books/McGraw-Hill. 2004.
- Yang SC, Cameron DE, editors. *Current therapy in thoracic and cardiovascular medicine*. McGraw-Hill Inc, 2004.

Ambulatory ECG

- Zimetbaum, P, Josephson, M. The Evolving Role of Ambulatory Arrhythmia Monitoring in General Clinical Practice. *Annals of Internal Medicine*. 130 (10). 1999.
- Kadish AH, Buxton AE, Kennedy HL. ACC/AHA clinical competence statement on electrocardiography and ambulatory electrocardiography: a report of the ACC/AHA/ACP-ASIM task force on clinical competence. *Circulation*. 104:3169-3178. 2001.
- Krahn, A., Klein, G., Skanes, A., Yee, R. Insertable Loop Recorder Use for Detection of Intermittent Arrhythmias. *Pacing and Clinical Electrophysiology*. 27 (5). 2004.

Stress Testing

- Allison, T., Bardsley, W., Behrenbeck, T., Christian, T., Clements, I., Edwards, B., Gibbons, R., Miller, T., Oh, J., Pellicka, P., Roger, V., Squires, R., Weissler, A. 1996 Mayo Foundation for Medical Education and Research. 71(1): 43-52. 1996.
- Gibbons et al. Exercise Testing Guidelines. *JACC*. 30 (1):260-315. 1997.

Echocardiography

- Picano, E. Stress Echocardiography: A historical perspective. *Am J Med*. 114:126-130. 2003.
- Heatlie, G., Giles, M. Echocardiography and the general physician. *Postgrad Med. J.* 80:84-88. 2004.
- Cheitlin, M. ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography: Summary Article. *Journal of the American Society of Echocardiography*. 16 (10). 2003.
- Gowda, R., Khan, I., Sacchi, T., Patel, R. History of the evolution of echocardiography. *International Journal of Cardiology*. 97 (1): 1-6. 2004.

Nuclear Cardiology

- Sabharwal, N., Lahiri, A. Role of myocardial perfusion imaging for risk stratification in suspected or known coronary artery disease. *Heart*. 89:1291-1297. 2003.
- Beller, G., Zaret, B. Contributions of Nuclear Cardiology to Diagnosis and Prognosis of Patients with Coronary Artery Disease. *Circulation*. 2000.

MR

- Kim, WY, et al. Coronary magnetic resonance angiography for the detection of coronary stenoses. *NEJM*. 345(26):1863-9. 2001.
- Danias, P., Roussakis, A., Ioannidis J. Cardiac imaging Diagnostic performance of coronary magnetic resonance angiography as compared against conventional x-ray angiography A meta-analysis *Journal of the American College of Cardiology* 44(2): 1867-1876. 2004.

CT

- Miller JM et al. Diagnostic performance of coronary angiography by 64-row CT. *NEJM*. 359(22):2324-36. 2008.
- Schoepf, J., Becker, C., Ohnesorge, B., Yucel, K. CT of Coronary Artery Disease. *Radiology*. 232:18-37. 2004.
- Somberg, J. Arrhythmia Therapy. Lippincott Williams & Wilkins, Inc. 9(6): 537-542. 2002.

Cath/EPs

- Hayes, D., Furman, S. Cardiac Pacing: How it Started, Where We Are, Where We Are Going. *Journal of Cardiovascular Electrophysiology*. 15 (5) 2004.
- Zipes et al. ACC/AHA Task Force Report Guidelines for Clinical Intracardiac Electrophysiological and Catheter Ablation Procedures. *JACC*. 26 (2): 555-573. 1995.
- Wellens, J. Cardiac Arrhythmias: the quest for a cure. *Journal of the American College of Cardiology*. 44 (6): 1155-1163. 2004.
- Conti, J. ACC 2005 Annual Session Highlight. Cardiac Arrhythmias. *Journal of the American College of Cardiology*. 45 (11):B30-B32. 2005.
- Kean, D. New Catheter Ablation Techniques for the Treatment of Cardiac Arrhythmias. *Cardiac Electrophysiology Review*. 6:341-348. 2002.
- Skanes, A., Klein, G., Krahn, A., Yee, R. Cryoablation: Potentials and Pitfalls. *J Cardiovasc Electrophysiol*. 15:528-534. 2004.
- Packer, D. Evolution of Mapping and Anatomic Imaging of Cardiac Arrhythmias. *Journal of Cardiovascular Electrophysiology*. 15 (7). 2004.
- Zipes, D. The year in electrophysiology. *Journal of the American College of Cardiology*. 43 (7):1306-1324. 2004.
- Ryan TJ, Faxon DP, Gunnar RM, et al. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). *Circulation* 78(2):486-502. 1988.

Arrhythmias

- Bernstein AD. The NASPE/BPEG Pacemaker Code. *Tex Heart Inst J*. 1991; 18(4): 299-300.
- Garcia TB and Miller GT. Arrhythmia Recognition: The Art of Interpretation. 2004. Jones & Bartlett Publishers, Sudbury, MA.
- Prystowsky EN. Electrophysiology and Pacing. In: Textbook of Cardiovascular Medicine Third Edition, Topol EJ, Califf RM, Prystowsky EN, Thomas JD, Thompson PD Eds 2007. Lippincott Williams & Wilkins, Philadelphia, PA.

Percutaneous Angiography/PCI

- Guidelines for percutaneous transluminal coronary angioplasty: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures Subcommittee on Percutaneous Transluminal Coronary angioplasty). *J Am Coll Cardiol*. 12:529-545. 1988.
- O'Neill W., Dixon, S., Grines, C. The year in interventional cardiology. *Journal of the American College of Cardiology*. 45 (7):1117-1134. 2005.
- Bashore et al. ACC/SCAI expert consensus document. American College of Cardiology/Society for Cardiac Angiography and Interventions Clinical Expert Consensus Document on Cardiac Catheterization Laboratory Standards. *Journal of the American College of Cardiology*. 37 (8):2170-2214. 2001.
- Baim, D. New devices for percutaneous coronary intervention are rapidly making bypass surgery obsolete. *Lippincott Williams & Wilkins, Inc*. 19(6): 593-597. 2004.
- Serruys PW et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *NEJM*. 360(10):961-72. 2009.

Cardiovascular Surgery

- www.acc.org – The American College of Cardiology (clinical guidelines, etc)
- www.theheart.org – Cardiology Online (requires registration)
- www.heartvalverepair.net – Heart Valve Repair Online
- Alexander P and Giangola G. Deep venous thrombosis and pulmonary embolism: Diagnosis, prophylaxis, and treatment. *Ann Vasc Surg* 13: 318-27, 1999.
- Beard JD. Chronic lower limb ischemia. *BMJ*. 2000;320:854-857.
- Bojar RM. Manual of perioperative care in cardiac surgery, 3rd edition. Massachusetts: Blackwell Science Inc., 1999.
- Cheng DCH, David TE eds. Perioperative care in cardiac anesthesia and surgery. Austin: Landes Bioscience, 1999.
- Coulam CH and Rubin GD. Acute aortic abnormalities. *Semin Roentgenol* 36: 148-64, 2001.
- Crawford ES and Crawford JL. Thoracoabdominal Aortic Aneurysm. In: Vascular surgery: Principles and Practice 2nd edition, Veith FJ, Hobson RW, Williams RA, and Wilson SE Eds 1994. McGraw-Hill Inc, Toronto.
- Fuchs JA. Atherogenesis and the Medical Management of Atherosclerosis. In Vascular Surgery 4th edition, Robert B. Rutherford Ed. 1995. WB Saunders Co., Toronto. pp 222-234.
- Freischlag JA. Abdominal Aortic Aneurysms. In: Vascular surgery: Principles and Practice 2nd edition, Veith FJ, Hobson RW, Williams RA, and Wilson SE Eds 1994. McGraw-Hill Inc, Toronto.
- Hallett JW Jr. Abdominal aortic aneurysm: natural history and treatment. *Heart Dis Stroke* 1: 303-8, 1992.
- Hallett JW Jr. Management of abdominal aortic aneurysms. *Mayo Clin Proc* 75: 395-9, 2000.
- Harlan BJ, Starr A, Harwin FM. Illustrated handbook of cardiac surgery. New York: Springer-Verlag Inc., 1996.
- May J, White GH, and Harris JP. The complications and downside of endovascular therapies. *Adv Surg* 35: 153-72, 2001.
- Pitt MPI and Bonser RS. The natural history of thoracic aortic aneurysm disease: An overview. *J Card Surg* 12(Suppl): 270-8, 1997.
- Powell JT and Brown LC. The natural history of abdominal aortic aneurysms and their risk of rupture. *Adv Surg* 35: 173-85, 2001.
- Rosen CL and Tracy JA. The diagnosis of lower extremity deep venous thrombosis. *Em Med Clin N Am* 19: 895-912, 2001.
- Schmieder FA and Comerota AJ. Intermittent claudication: magnitude of the problem, patient evaluation, and therapeutic strategies. *Am J Card* 87 (Suppl): 3D-13D, 2001.
- Verma S, Szmikko PE, et al. Clinician Update: Should radial arteries be used routinely for coronary artery bypass grafting? *Circulation*. 2004;110:e40-e46.
- Way LW, Doherty GM, editors. Current Surgical Diagnosis and Treatment, 11th edition. Lange Medical Books/McGraw-Hill. 2004.
- Yang SC, Cameron DE, editors. Current therapy in thoracic and cardiovascular medicine. McGraw-Hill Inc, 2004.

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Agonists			
Antagonists			
Effectiveness and Safety			
Therapeutic Index (TI)			

General Principles

Drug Nomenclature

- chemical name: describes the chemical structure; the same in all countries
 - e.g. N (4-hydroxyphenyl) acetamide is acetaminophen
- drug company code: a number; usually for drugs that are not yet marketed
- non-proprietary (generic) name: shortened form of chemical name; listed in pharmacopoeia
 - e.g. acetaminophen
- proprietary (trade) name: the brand name or registered trademark
 - e.g. Tylenol®
- street name: slang term used for a drug of abuse

Phases of Clinical Testing

- phase I: first administration to healthy human volunteers, following animal studies; to determine pharmacokinetics and pharmacodynamics
- phase II: first administration to patients, small studies; to determine therapeutic efficacy, dose range, pharmacokinetics, pharmacodynamics
- phase III: large sample, often double-blind RCT; to compare a new drug to placebo or standard of care, establish safety and efficacy
- phase IV: post-marketing surveillance, wide distribution; to determine rare adverse reactions, effects of long-term use, determine ideal dosing

Drug Administration and Site of Action

- choice of route of administration depends on
 - properties of the drug
 - local and systemic effects (limiting action or adverse events)
 - desired onset and/or duration of action
 - patient characteristics

Table 1. Routes of Drug Administration

Route	Advantage	Disadvantage
Oral (PO)	Convenient, easy to administer Large surface area for absorption Inexpensive relative to parenteral administration	Drug metabolism by GI secretions Incomplete absorption Hepatic first-pass effect Potential GI irritation
Buccal Sublingual (SL)	Rapid onset of action No hepatic first-pass effect	Must be lipid soluble Must be non-irritating Short duration of action
Rectal (PR)	Almost no hepatic first-pass effect Convenient if patient is NPO, vomiting or unconscious	Inconvenient Irritation at site of application Erratic absorption
Intravenous (IV)	Direct to systemic circulation No hepatic first-pass effect Slow infusion or rapid onset of action Easy to titrate dose	Requires IV access, aseptic technique Hard to remove once administered Vascular injury, extravasation Expensive Risk of infection, bleeding
Intra-arterial	Direct to specific organs (heart, brain) No hepatic first-pass effect	Risk of infection, bleeding, vascular complications
Intramuscular (IM)	Depot storage if oil-based = slow release of drug Aqueous solution = rapid onset of action	Pain at site of injection
Subcutaneous (SC)	Non-irritating drugs, small volumes Constant, even absorption Alternative to IV	Pain at site of injection Smaller volumes than IM May have tissue damage from multiple injections
Intrathecal	Direct into cerebrospinal fluid (CSF) Bypass BBB and blood-CSF barrier	Infection Possibility of brain herniation and coning



At the time of drug launch, only data from phases I-III are available; thus true effectiveness (in contrast to efficacy) and safety may be unknown, because real-world patients and usage patterns often do not reflect premarket phase.



Common Latin Abbreviations

q	each, every
od/bid/tid/qid	once/twice/three/four times a day
hs	at bedtime
ac/pcc/cc	before/after/with meals
prn	as necessary
gtt	drops
ung	ointment
ud	as directed
od/os/ou	right/left/each eye
ad/as/au	right/left/each ear

Table 1. Routes of Drug Administration (continued)

Route	Advantage	Disadvantage
Inhalation	Immediate action in lungs Rapid delivery to blood Local or systemic action No hepatic first-pass effect	Must be a gas, vapour or aerosol
Topical	Easy to administer Localized Limited systemic absorption	Effects are mainly limited to site of application
Transdermal	Drug absorption through intact skin Rapid onset of action No hepatic first-pass effect	Irritation at site of application Delayed onset of action Hydrophilic drugs are not easily absorbed
Others: Intraperitoneal, Intra-articular	Local effect	Risk of infection

Overview of Drug Disposition

Pharmacology = Pharmacokinetics + Pharmacodynamics

Pharmacokinetics

- the study of “what the body does to a drug;” the fate of a drug in the body
- subdivided into ADME: absorption, distribution, metabolism and elimination

Pharmacodynamics

- the study of “what a drug does to the body;” the interaction of a drug with its receptor and the resultant effect
- includes dose-response relationship, drug-receptor binding

Pharmacokinetics (ADME)

- definition: relationship between drug administration, time-course of distribution, and concentration achieved in the body (i.e. the manner in which the body handles a drug)
- examines rate and extent at which drug level concentrations change in the body by observing:
 - input processes = absorption
 - output processes responsible for drug delivery and removal from the body = distribution, metabolism, elimination

Absorption

- definition: movement of the drug from the site of administration into plasma
- important for the main routes of administration, except IV

Mechanisms of Drug Absorption

- most drugs are absorbed into the systemic circulation via passive diffusion
- other mechanisms: active transport, facilitated diffusion, pinocytosis/phagocytosis

Factors Affecting the Rate and Extent of Drug Absorption

- partition coefficient of a drug ($P_{\text{oil/water}}$), i.e. its relative solubility in oil (lipid) vs. water
 - drugs with high lipid solubility can rapidly diffuse across a cell membrane (e.g. anaesthetics are very lipid soluble and thus have a rapid onset of action)
- local blood flow at the site of administration (e.g. sublingual vessels provide significant blood flow and thus rapid absorption)
- molecular size (e.g. small molecular weight drugs absorb faster)
- pH and drug ionization
 - drugs are usually weak acids (e.g. acetylsalicylic acid) or weak bases (e.g. ketoconazole) and thus have both ionized and non-ionized forms
 - pH and pK_a determine the ratio of ionized:non-ionized ratio (using the Henderson-Hasselbach equation)
 - non-ionized forms cross cell membranes much faster than ionized (charged) forms
- total surface area for absorption
 - the small intestine has villi, which increase the surface area for absorption, making it the primary site of absorption for most oral drugs



Partition Coefficient (P)

- The ratio of a drug's solubility in lipid as compared to water
- More relevant when thought of in terms of a drug's solubility in membrane as compared to extracellular fluid
- A large P means that a drug is highly soluble in lipid and will thus cross membranes easily



Drug Ionization and the Henderson-Hasselbach Equation

Ionization reaction for a weak acid:
 $HA \rightleftharpoons A^- + H^+$; $pK_a = pH + \log [HA/A^-]$
 (Henderson-Hasselbach equation)

For a weak acid of $pK_a = 4.4$,
 at a gastric pH of 1.4,
 non-ionized:ionized = $HA:A^- = 1:0.001$

Thus, the drug is mainly non-ionized and diffuses across membrane

Ionization reaction for a weak base:
 $BH^+ \rightleftharpoons B + H^+$; $pK_a = pH + \log [BH^+/B]$



The amount of drug that reaches the systemic circulation (bioavailability) is highly dependent on absorption and the first-pass effect. Properties of the drug, route of administration and patient factors should be considered to ensure clinical effectiveness.

Bioavailability (F)

- definition: drug fraction of administered dose that reaches systemic circulation in an unchanged state after administration
- factors affecting bioavailability:
 - drug absorption, metabolism in the gut wall, and hepatic first-pass effect
- IV dose have 100% bioavailability ($F = 1$)
- drugs with a low bioavailability may require a much a much larger oral dose when compared to the intravenous dose (e.g. beta-blockers: metoprolol 5 mg IV vs. metoprolol 50 mg PO)

Hepatic First-Pass Effect

- definition: drug metabolism by the liver following absorption, but before it reaches systemic circulation
- occurs with PO administration of a drug: GI tract (absorption) → portal vein in liver (first-pass metabolism) → systemic circulation; significant first-pass effect can drastically reduce a drug's bioavailability
- occurs to much lesser extent with PR administration, because drug absorbed in colon bypasses the portal system: colon (absorption) → internal pudendal veins → IVC → systemic circulation
- drugs with a high hepatic first-pass effect (hepatic extraction) include:
 - levodopa, morphine, propranolol, lidocaine, organic nitrates
- drugs with low hepatic extraction (little or no first-pass effect) include:
 - diazepam, digoxin, phenytoin, warfarin

Efflux Pump

- P-glycoprotein (Pgp) is a protein in the GI tract and renal epithelium that acts as a multidrug efflux pump involved in the transport of drugs out of cells
 - i.e. reduced intestinal absorption and enhanced renal elimination of certain drugs
- examples of Pgp substrates:
 - digoxin, etoposide, paclitaxel, tacrolimus
- some drugs (e.g. macrolide antibiotics) inhibit Pgp and can increase absorption of Pgp substrates and reduce their renal elimination
- some tumours overexpress Pgp leading to multi-drug resistance to chemotherapy agents

Distribution

- definition: process by which drugs move between different body compartments and to the site of action
- major body fluid compartments: plasma, interstitial fluid, intracellular fluid, transcellular fluid (e.g. CSF, peritoneal, pleural)
- tissue compartments: fat, brain

Factors Affecting the Rate and Extent of Drug Distribution

- physicochemical properties of the drug (e.g. partition coefficient)
- pH of fluid
- plasma protein binding
- binding within compartments
- cardiac output
- regional blood flow
- percentage body fat

Volume of Distribution (V_d)

- maximum "actual V_d " = total body water (40 L for average adult) (see Figure 1)
- V_d : the apparent volume of fluid into which a drug dissolves
 - relates amount of drug in the body to the plasma concentration
 - a calculated value that does not correspond to an anatomical space (when calculated, V_d can exceed a person's total body water or 40 L)
 - the value takes into account drug distribution into tissues and protein binding
 - volume of distribution of plasma-protein bound drugs can be altered by liver and kidney disease
 - $V_d = \text{amount of drug in body} / \text{plasma drug concentration}$
- example: amiodarone distributes into total body water (TBW = actual $V_d = 40$ L), but it also concentrates in fat tissues giving instead an apparent V_d of 400 L; i.e. to achieve a given plasma concentration of amiodarone, we dose as if the drug distributes into 400 L of body fluid

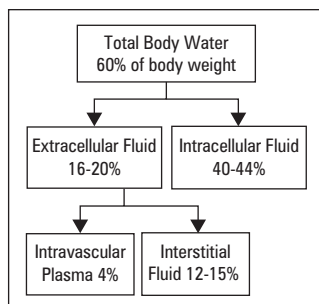


Figure 1. Distribution of Total Body Water (TBW)

Principles of Protein Binding

- drug molecules in the blood exist in two forms:
 1. bound to plasma proteins
 - ♦ acidic drugs bind to albumin
 - ♦ basic drugs bind to α_1 -acid glycoprotein
 2. free or unbound
 - ♦ only free drug can leave the circulation to distribute into tissues and exert an effect; free drug is subject to metabolism and elimination

- in plasma, the fractions of free and bound drugs exist in equilibrium, i.e. as free drug leaves the circulation, more drug unbinds to equilibrate with the portion that is left
- the fraction of drug that is bound is determined by
 - drug concentration, drug affinity for protein binding site, and number of binding sites or protein concentration
- saturation of binding sites may result in a large increase in free drug concentration, potentially leading to toxicity
- in hypoalbuminemia (liver failure or nephrotic syndrome), the dose of some highly bound drugs must be lowered to avoid toxicity
- multiple drugs and endogenous substances can compete for the same protein binding sites, leading to increased free drug concentration but it is rarely of clinical significance
 - e.g. ASA displaces highly protein bound acidic drugs such as phenytoin, thus possibly increasing the risk of toxicity; sulfonamide displaces bilirubin from protein binding sites, which could potentially lead to jaundice and kernicterus in neonates
- usually only highly protein bound (>90%) drugs are involved in drug interactions due to competitive binding; however, plasma protein binding interactions are rarely of clinical significance

Depots

- a body compartment (i.e. a type of tissue) where drug molecules tend to be stored and released slowly over a long period of time
- fat is a depot for very lipid soluble drugs (e.g. diazepam)
- some oil-based medications are injected IM for slow release (e.g. depot medroxyprogesterone acetate q3mo; depot risperidone q2wks)

Barriers (relative)

- body structures that limit or prevent diffusion of drug molecules
 - e.g. the placenta or blood brain barrier (BBB; a barrier composed of tight junctions between capillary endothelial cells and astrocytes)
- many of these barriers result, in part, from the activity of multidrug efflux pumps (e.g. Pgp) which serve as a natural defense mechanism against drugs and xenobiotics
- need to consider dosing route if drugs are meant to cross these barriers

Metabolism (Biotransformation)

- definition: chemical transformation of a drug *in vivo*
- sites of biotransformation: liver (main), GI tract, lung, plasma, kidney
- goal is to make compounds more hydrophilic to enhance renal elimination
- as a result of the process of biotransformation:
 - a pro-drug may be **activated** to an active drug (e.g. tamoxifen to endoxifen)
 - a drug may be **changed** to another active metabolite (e.g. diazepam to oxazepam)
 - a drug may be **changed** to a toxic metabolite (e.g. meperidine to normeperidine)
 - a drug may be **inactivated** (e.g. procaine to PABA)

Drug Metabolizing Pathways

- phase I (P450) reactions
 - small molecular changes introduce or unmask polar chemical groups on a parent compound to increase its water solubility (e.g. oxidation-reduction, hydrolysis, hydroxylation); the change in the partition coefficient is typically minimal (demethylation, deamination, hydroxylation) compared to phase II, and often phase I places a polar 'handle' on a lipophilic drug to allow for phase II
 - mediated by cytochrome P450 enzymes found in the endoplasmic reticulum or cell cytoplasm
 - product of the reaction can be excreted or undergo further phase II reactions
- phase II (conjugation) reactions
 - conjugation with large polar endogenous substrates (e.g. glucuronidation, glutathione conjugation, sulfation)
 - dramatically increases water solubility and renal elimination

Factors Affecting Drug Biotransformation

- **genetic polymorphism** of metabolizing enzymes
 - individuals may metabolize drugs faster or slower depending on their genotype, resulting in poor, intermediate, extensive or ultrarapid metabolizers
 - may lead to toxicity or ineffectiveness of a drug at a normal dose (e.g. tamoxifen and codeine are prodrugs activated by 2D6 (nonfunctional alleles reduce effectiveness), while warfarin metabolized by 2C9 (nonfunctional alleles lead to lower dose requirements))



Special consideration must be given in dosing patients in hypoalbuminemic states to prevent drug toxicity. Highly protein-bound drugs will exert a greater effect in these patients than in healthy individuals because of higher levels of free drug.

Examples of highly protein-binding drugs: warfarin, digoxin, diazepam, furosemide, amitriptyline.



Main Factors Governing Penetration of Blood Brain Barrier (BBB)

1. Small molecular size (<500 Daltons)
2. High lipid solubility
3. Active transport mechanisms (e.g. Pgp multidrug efflux pump)

Many Drugs Cross BBB. Examples:

- General anesthetics
- Alcohol
- Nicotine
- Caffeine
- L-dopa
- Narcotics
- Psychotropic medications



Cytochrome P450 System

The P450 enzymes are a superfamily of heme proteins that are grouped into families and subfamilies according to their amino acid sequence. These proteins are responsible for the metabolism of drugs, chemicals and other substances.

Nomenclature: CYP3A4
"CYP" = cytochrome P450 protein

1st number = family
letter = subfamily
2nd number = isoform

The CYP1, CYP2, and CYP3 families metabolize most drugs in humans. The most important isoforms are CYP3A4 and CYP2D6; therefore, anticipate drug interactions if prescribing drugs using these enzymes.



Some Common Examples of P450 Inhibitors and Inducers

P450 inhibitors "MINCE"

Metronidazole
Isoniazid, Indinavir
Naringin or bergamottin (bioflavonoid in grapefruit)
Ciprofloxacin, Cimetidine
Erythromycin (macrolides)

P450 inducers

Phenytoin
Phenobarbital
Rifampin
Smoking

Note: Several medications are known to affect P450s. The above list is not exhaustive.



The very young and the very old are very sensitive to the actions of drugs.

- **enzyme inhibition** may sometimes be due to other drugs
 - e.g. CYP3A4 inhibition leads to an increased concentration of the substrate drug
 - erythromycin, ketoconazole and indinavir inhibit CYP3A4 and predispose a patient to drug toxicity from other drugs metabolized by it
 - grapefruit juice inhibits gut CYP3A4 and effectively increases a substrate's bioavailability
- **enzyme induction**
 - certain medications enhance gene transcription leading to an increase in the activity of a metabolizing enzyme
 - a single drug may stimulate multiple P450 isoenzymes simultaneously
 - a drug may induce its own metabolism (e.g. carbamazepine) or that of other drugs (e.g. phenobarbital can induce the metabolism of OCP and bilirubin) by inducing the P450 enzyme system
 - other potent enzyme inducers: phenytoin, dexamethasone
- **liver dysfunction** caused by disease (such as hepatitis, alcoholic liver, biliary cirrhosis or hepatocellular carcinoma) may decrease drug metabolism, but this may not be clinically significant due to the liver's reserve capacity
- **renal disease** often results in decreased drug clearance if it is cleared by the kidneys
- **extremes of age** (neonates or elderly) have reduced biotransformation capacity, and doses should be adjusted accordingly
- **nutrition**
 - insufficient protein and fatty acid intake decrease P450 biotransformation
 - vitamin and mineral deficiencies may also impact metabolizing enzymes
- **alcohol**: while acute alcohol ingestion inhibits 2E1, chronic consumption can induce this same enzyme and increase the risk of hepatocellular damage from acetaminophen by increasing the generation of acetaminophen's toxic metabolite
- **smoking** can induce 1A2, thus increasing the metabolism of some drugs (e.g. smokers may require higher doses of theophylline, which is metabolized by 1A2)

Elimination

- definition: removal of drug from the body

Routes of Drug Elimination

- kidney (main organ of elimination)
 - two mechanisms for renal elimination
 1. glomerular filtration
 - a passive process, so that only the free drug fraction can be filtered
 - drug filtration rate depends on GFR, degree of protein binding of drug, and size of drug
 2. tubular secretion
 - an active process that is saturable, allowing both protein-bound and free drug fractions to be excreted
 - two distinct transport mechanisms for weak acids (e.g. penicillin, salicylic acid, probenecid, chlorothiazide) and weak bases (e.g. quinine, quaternary ammonium compounds such as choline)
 - drugs may competitively block mutual secretion if both use the same secretion system (e.g. probenecid can be used to reduce the excretion of penicillin, thereby prolonging the half-life and thus the effect of the antibiotic)
 - tubular reabsorption: drugs can be passively reabsorbed back to the systemic circulation, countering elimination mechanisms
 - elimination rate depends on renal function, which decreases with age and is affected by many disease states; renal function is assessed clinically using serum creatinine (Cr) levels
 - thus, in those with renal impairment, dosage adjustments may be required for medications affected by renal elimination
- stool
 - some drugs and metabolites are actively excreted in the bile (e.g. corticosteroids) or directly into the intestinal tract from systemic circulation
 - enterohepatic circulation
 - ♦ counteracts stool elimination, and thus can substantially prolong the drug's duration in the body
 - ♦ some glucuronic acid conjugates that are excreted in the bile will be hydrolyzed in the intestines by bacteria; this results in the drug being converted back to its original form and allows for systemic reabsorption
- lungs
 - elimination of anesthetic gases and vapours by exhalation
- saliva
 - saliva concentrations of some drugs parallel their plasma levels (e.g. rifampin)



Avoid toxicity from drug or metabolite accumulation by adjusting a drug's dosage according to the elimination characteristics of the patient (e.g. in renal impairment).



The Cockcroft-Gault Equation can estimate creatinine clearance (CrCl) in adults 20 years of age and older:

- For males

$$\text{CrCl (mL/min)} = \frac{[(140 - \text{age in yrs}) \times \text{Weight (kg)}]}{\text{serum Cr (}\mu\text{mol/L)}} \times 1.2$$
- For females, multiply above equation x 0.85
- Only applies when renal function is at steady state

Pharmacokinetics Calculations

- definition: the quantitative description of the rates of the various steps of drug disposition, i.e. how drugs move through the body
- the pharmacokinetic principles of ADME (absorption, distribution, metabolism and elimination) can be graphically represented on the concentration vs. time graph (see Figure 2)

Time-Course of Drug Action

- many kinetic parameters are measured using IV dosing, such that absorption is zero and distribution for most drugs is rapid; thus elimination is the main process being measured
 - the concentration axis is converted to a \log_{10} concentration to allow for easier mathematical calculations (see Figure 3)

Half-Life ($t_{1/2}$)

- definition: time taken for the serum drug level to fall to 50% during elimination
- for drugs with first order kinetics, takes five half-lives to reach steady state with repeated dosing, or for drug elimination once dosing is stopped
- only applies when drug exhibits first order kinetics
- see sidebar for calculation

# of Half Lives	1	2	3	3.3	4	5
Concentration	50%	75%	87.5%	90%	93.8%	96.9%

Steady State

- the concentration at which the same amount of drug entering the system is eliminated from the system
- time is important for therapeutic monitoring since drug levels are reliable only when the drug has reached steady state (see Figure 4)
- special situations
 - use a loading dose for drugs with a long half-life and when there is clinical need to rapidly achieve therapeutic levels (e.g. amiodarone, digoxin, phenytoin)
 - use continuous infusion for drugs with a very short half-life and when there is need for a long-term effect and multiple or frequently repeated doses are too inconvenient (e.g. nitroprusside, insulin, unfractionated heparin)

Clearance (CL)

- a quantitative measurement of the rate of removal of a substance from the body
- relates the rate of elimination to the plasma concentration
- clearance = body fluid volume from which a substance is removed per unit time
- consider: clearance from a specific part of the body, and total body clearance
- CL = rate of elimination of drug/plasma drug concentration

Elimination Kinetics (see Figure 5)

- first-order kinetics (most common type)
 - linear and predictable relationship that leads to a constant fraction of drug eliminated per unit time
 - the amount of drug eliminated is based on the concentration of drug present
- zero-order kinetics (less common, associated with toxicities, e.g. alcohol)
 - non-linear kinetics that leads to a constant rate of drug eliminated regardless of concentration
 - clearance slows as drug concentration rises
 - some drugs can follow first-order kinetics until elimination is saturated (usually at large doses) at which point the clearance decreases
 - some drugs follow zero-order kinetics at therapeutic levels (e.g. phenytoin)

Table 2. Loading vs. Maintenance Dosing

Loading Dose	Maintenance Dose
Use when you need an IMMEDIATE effect	Consider either: after a loading dose OR beginning with maintenance doses
Often parenteral medication	Steady-state levels achieved after ~5 half lives
Rational: give large dose of medication to "fill up" the volume of distribution	Can be given as either a continuous infusion (relatively rare, short half-life drug) OR much more commonly as intermittent doses



Principles of Pharmacokinetics

V_d = amount of drug in the body/
plasma drug concentration

CL = rate of elimination of drug/plasma
drug concentration

Half-life ($t_{1/2}$) = $0.7 \times V_d / CL$



For most drugs, it takes 5 half-lives to reach steady state with repeated dosing or to eliminate a drug once dosing is stopped.

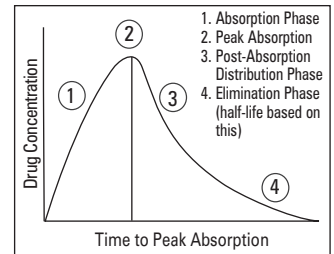


Figure 2. Time Course of Drug Action

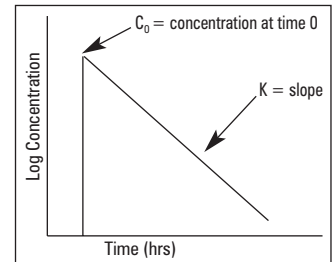


Figure 3. Log Concentration vs. Time Graph (IV bolus dose)

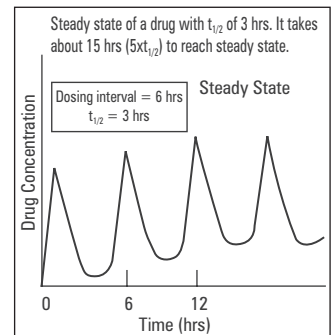


Figure 4. Steady State of a Drug

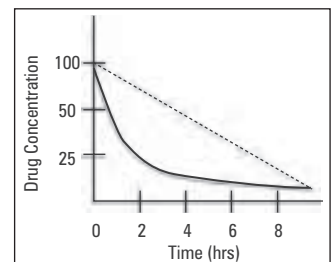


Figure 5. First and Zero Order Kinetics. In first order kinetics (solid line), a constant fraction of the drug is eliminated per unit time; in zero order kinetics (dashed line), a constant amount of the drug is eliminated per unit time.



For unit conversion factors, please see Appendix: Common Unit Conversions.

Pharmacodynamics

Dose-Response Relationship

- effectiveness and potency are two important pharmacodynamic characteristics of a drug that can be quantified using dose-response curves
- with gradual dose-response relationships, the response of the drug reflects the number of receptors that are effectively occupied

Effectiveness

- a measure of a drug's ability to elicit a concentration-independent effect at its receptor
- measured as E_{max} = the maximal **response** that a drug can elicit (see Figure 6)
- reflects drug response under ideal circumstances (e.g. controlled clinical trial)
- e.g. if Drug A causes a greater maximum intensity of response than Drug B regardless of dose, then Drug A is more efficacious than Drug B

Potency

- a measure of the effect produced by a certain drug concentration
- measured as ED_{50} (or EC_{50}) = the **effective concentration** of a drug needed to produce 50% of the maximal possible effect (see Figure 6)
- can compare the ED_{50} of two or more drugs that have parallel log dose-response curves
- the drug that reaches its ED_{50} at the lower dose is the more potent
- if the potency of a drug is low, this may be overcome by increasing the dose of the drug (e.g. 30 mg vs. 15 mg); this is not problematic provided that the higher dose not cause adverse effects



Effectiveness versus Potency

- Effectiveness measures a drug's maximal effect and is independent of concentration.
- Potency measures a drug's concentration needed to produce a certain effect.

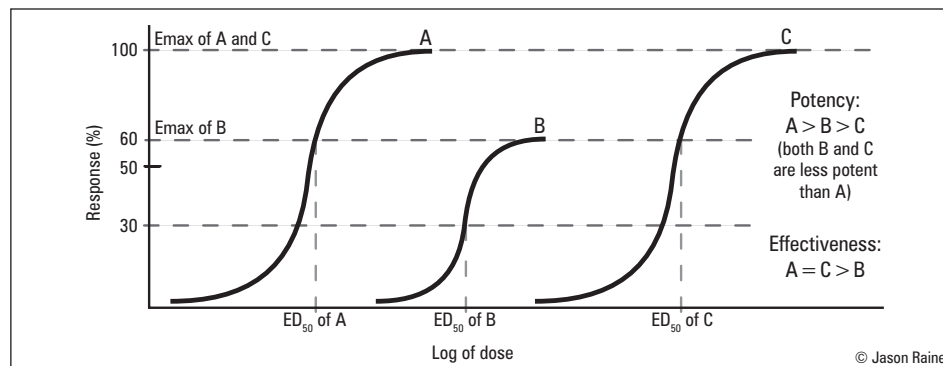


Figure 6. Log Dose-Response Curve Illustrating Effectiveness and Potency

Effects of Drugs on Receptors

- drugs that act on specific receptors can be broadly classified as agonists or antagonists (see Figure 7)

Agonists

- drugs that mimic endogenous ligands and exert an effect
- have two main properties
 - affinity: the ability of the agonist to bind to the receptor (e.g. the β_2 -agonist salbutamol has greater affinity for β_2 -receptors than β_1 -receptors)
 - efficacy: the ability to cause a response via the receptor interaction (e.g. binding of salbutamol to β_2 -receptors results in smooth muscle relaxation)
- full agonists: can elicit a maximal effect at a receptor
- partial agonists: can only elicit a partial effect, no matter how high the concentration
 - e.g. reduced efficacy compared to full agonists

Antagonists

- drugs that have affinity (can bind to a receptor), but no efficacy
- these are drugs that block the action of an agonist or of an endogenous ligand
- chemical antagonism:** direct chemical interaction between agonist and antagonist that prevents agonist binding to receptor
 - e.g. chelating agents for removal of heavy metals

- **functional antagonism:** interaction of two agonists that act independently at different receptors but have opposite physiological effects
 - e.g. acetylcholine at the muscarinic receptor decreases HR, constricts pupils, and stimulates intestinal motility; whereas epinephrine at the adrenergic receptor increases HR, dilates pupils, and decreases intestinal motility
- **reversible competitive antagonism** (most common in clinical practice, see Figure 8)
 - antagonist reversibly binds to the same receptor as the agonist, thus displacing it (e.g. naloxone is an antagonist to morphine or heroin)
- **irreversible competitive antagonism** (see Figure 9)
 - antagonist irreversibly binds to the same receptor as the agonist, blocking it from binding (e.g. acetylsalicylic acid irreversibly binds cyclo-oxygenase in platelets)
- **non-competitive antagonism** (see Figure 9)
 - antagonist binds to an alternate site separate but near to the agonist receptor, producing allosteric effects that change the ability of the agonist to bind (e.g. organophosphates irreversibly bind acetylcholinesterase)

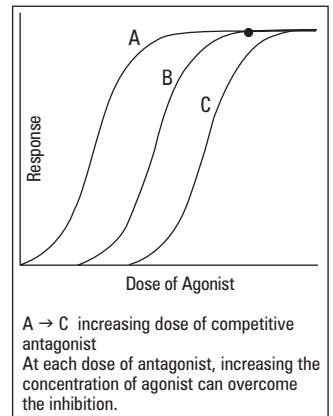


Figure 8. The Log Dose-Response Curve for Competitive Reversible Antagonism

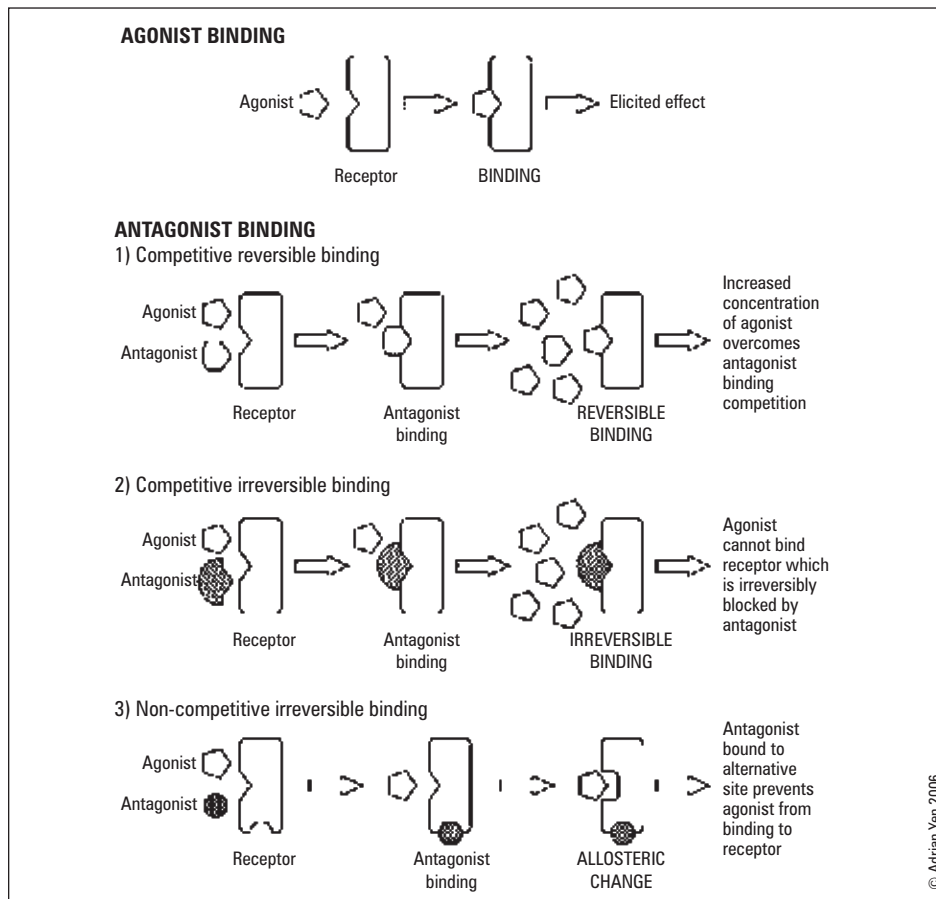


Figure 7. Mechanism of Agonists and Antagonists

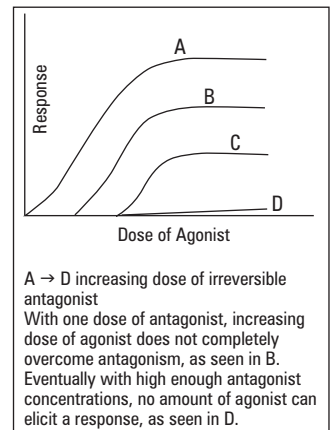


Figure 9. The Log Dose-Response Curve for Irreversible Antagonism

Effectiveness and Safety

Effectiveness

- ED_{50} (Effective Dose – 50%): the dose of a drug needed to cause a therapeutic effect in 50% of a test population of subjects

Safety

- LD_{50} (Lethal Dose – 50%): the dose of a drug needed to cause death in 50% of a test population of subjects (usually rodents)
- TD_{50} (Toxic Dose – 50%): the dose needed to cause a harmful effect in 50% of a test population of subjects



The two most clinically relevant properties of any drug are effectiveness and safety.



Drugs with a narrow TI have a high likelihood of causing toxicity and need close therapeutic monitoring.

Therapeutic Index (TI)

- defined as TD_{50}/ED_{50} (see Figure 10)
- reflects the “margin of safety” for a drug – the likelihood of a high dose causing serious toxicity or death
- the larger the TI, the safer a drug (e.g. amoxicillin has a wide TI, thus therapeutic monitoring is not needed, whereas warfarin has a narrow TI and must have accurate therapeutic monitoring)
- factors that can change the ED_{50} , LD_{50} or TD_{50}
 - presence of interacting drugs
 - changes in drug absorption, distribution, metabolism, elimination

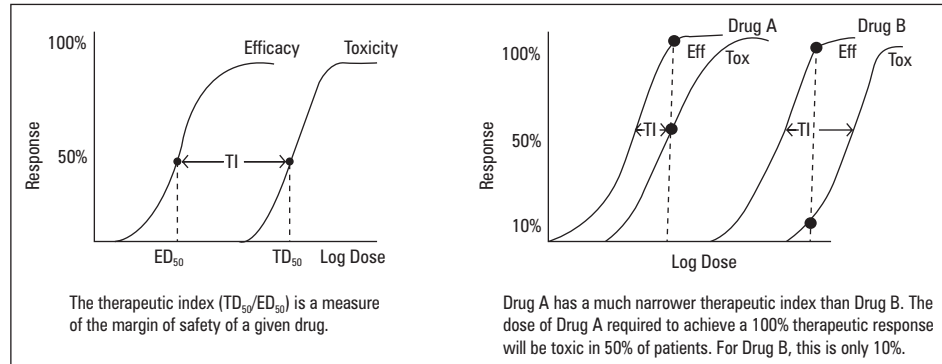


Figure 10. ED_{50} , TD_{50} , and the Therapeutic Index (TI)

Therapeutic Drug Monitoring (TDM)

- definition: using serum drug concentration data to optimize drug therapy (e.g. dose adjustment, monitor compliance)
 - serum drug samples are usually taken when the drug has reached steady state (e.g. trough level – the lowest level before the next dose), and thus, before the next dose
- TDM can serve to monitor for side effects (e.g. vancomycin trough levels) and for desired effect (e.g. INR when on warfarin therapy)
- TDM is often used for drugs that have
 - narrow therapeutic index (TI)
 - unpredictable dose-response relationship
 - significant consequences associated with therapeutic failure or toxicity
 - wide inter-patient pharmacokinetic variability

Adverse Drug Reactions (ADRs)

- classification of adverse drug reactions
 - type A: undesirable normal/augmented responses to the drug (>80% of all ADRs)
 - type B: reaction unrelated to the known pharmacological actions of the drug
- additional adverse drug reaction categories
 - type C (chronic effects), type D (delayed effects), type E (end-of-treatment effects), and type F (failure of therapy)

Table 3. Comparison of characteristics of type A and type B reactions

Type A	Type B
Predictable extension of drug's pharmacologic effect	Unpredictable
Usually dose dependent	Rarely dose dependent
Low mortality (except heroin overdose)	High mortality (some exceptions)
Responds to dose reduction	Responds to drug withdrawal



Examples of drugs whose levels need to be monitored: warfarin (via INR levels), digoxin, lithium, and many others.



In Canada, an estimated 1.6% of patients admitted to hospitals experience a serious adverse drug reaction. Furthermore, up to 24% of hospitalizations are drug related, of which 35.5% are adverse drug reactions.

Type A Drug Reactions

- extension of a drug's pharmacological effects: excessive but characteristic pharmacological effect from usual dose of a drug (e.g. beta-blockers causing bradycardia; acetaminophen causing hepatitis)
- overdose/toxicity: exaggerated but characteristic pharmacological effect from SUPRA-therapeutic dose
- teratogen: drug may produce developmental defects in fetus (not always in a dose-related manner)

Type B Drug Reactions

- idiosyncratic: uncharacteristic response to drug, unrelated to pharmacology (e.g. sulfa-containing medications causing toxic epidermal necrolysis)
- pseudoallergenic: mimics immune-mediated reaction
- allergic/immune-mediated: does not occur on first exposure (up to 7 d), immediate with subsequent exposure, may occur with low doses, often resolves within 3-4 days of discontinuation



Sulfa-Containing Medications

- Sulfamethoxazole
- Sulfasalazine
- Dapsone

Approach to Suspected ADRs

- history and physical examination: signs and symptoms of the reaction (e.g. rash, fever, hepatitis, anaphylaxis, etc.), timing, risk factors, detailed medication history including all drugs and timing, dechallenge (response when drug is removed) and rechallenge (response when drug is given again)
- check with literature, Health Canada and FDA; contact the pharmaceutical company
- differentiate between drug therapy vs. disease pathophysiology
- treatment: stop the drug, supportive care, symptomatic relief
- Canadian Adverse Drug Reaction Monitoring Program online
- report all suspected ADRs that are: 1) unexpected, 2) serious, or 3) reactions to recently marketed drugs (on the market <5 years) regardless of nature or severity

Table 4. Sample of Clinically Relevant Adverse Drug Reactions and Interactions

Classification	Drug(s)	Adverse Drug Reaction	Comments
A	Beta-blockers	Bradycardia	Dose dependent
A	ACEI	Cough	Switch ACEI to ARB
B	Vancomycin	Red Man Syndrome	Pruritic erythematous rash on upper body related to rapid infusion of first dose Not considered "allergy"
B	Sulfa Drugs	Stevens-Johnson Syndrome Toxic Epidermal Necrolysis	Life threatening; do not rechallenge under any circumstance
B	Penicillin	Rash	Many children with EBV infection will develop a rash when given amoxicillin; this is NOT a true penicillin allergy
B	Aminoglycosides	Ototoxicity and nephrotoxicity	Dose dependent
B	Acetaminophen, Valproic acid, Chinese herbs	Hepatotoxicity	Many other drugs are hepatotoxic (e.g. statins, OCPs, isoniazid)

Variability in Drug Response

- recommended patient dosing is based on clinical research and represents mean values for a select population, but each person may be unique in their dosing requirements
 - the majority (but not all) of the patients will experience the desired therapeutic effect of a drug with minimal ADRs on the recommended dose
 - may need to adjust dosing or alter medication altogether
- there may be multiple causes of individual variability in drug response at a given dose, and they should be considered when prescribing and dosing medications

- possible causes of variable drug responses include problems with:
 - intake
 - patient adherence, e.g. hard to follow dosing schedule, non-palatable drug, costly drug
 - pharmacokinetics
 - absorption
 - decreased by vomiting, diarrhea or steatorrhea
 - hepatic first pass effect too high due to enzyme induction, or too low due to liver disease
 - absorption change due to drug interactions (e.g. calcium carbonate chelates iron)
 - distribution
 - very high or low percentage body fat, intact or disrupted BBB metabolism
 - patient is elderly or a neonate, or has liver dysfunction
 - certain genetic polymorphisms or lack of enzymes to metabolize drugs (e.g. acetylcholinesterase deficiency, CYP polymorphism)
 - metabolism increased by enzymatic induction or decreased by enzymatic inhibition
 - elimination
 - kidney or liver dysfunction, or obstruction of bile elimination pathway
 - pharmacodynamics
 - genetic variability in drug response (e.g. malignant hyperthermia due to specific anesthetic agents)
 - drug interactions (e.g. polypharmacy) or disease process that affects drug pharmacodynamics
 - drug tolerance

Autonomic Pharmacology

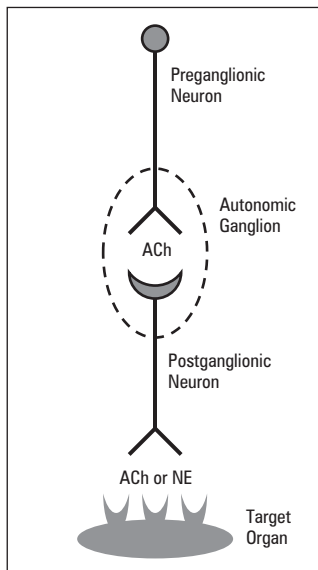


Figure 12. Autonomic Nervous System (ANS) Efferent Tracts

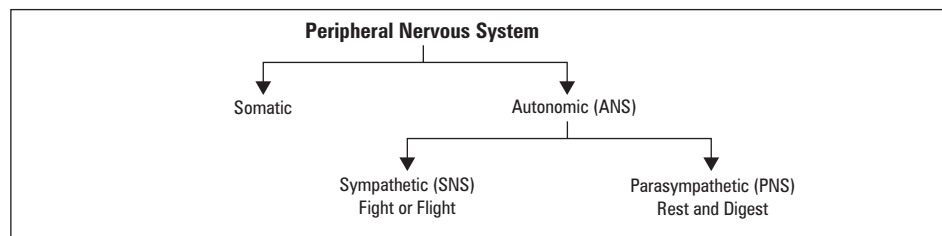


Figure 11. Subdivisions of the Peripheral Nervous System

- most organs are innervated by both sympathetic and parasympathetic nerves; these have opposing effects (see Figure 13)
- almost all ANS efferent tracts are divided into preganglionic and postganglionic nerves, which synapse in the autonomic ganglion (see Figure 12)
- sympathetic preganglionic fibers originate in the spinal cord at spinal levels T1-L3, and terminate in one of two ganglia
 - paravertebral ganglia, i.e. the sympathetic trunk, that lie in a chain close to the vertebral column
 - pre-vertebral ganglia, i.e. celiac and mesenteric ganglia, that lie within the abdomen
- parasympathetic preganglionic fibers originate in the lower brainstem from cranial nerves III, VII, IX, X, and in the sacral spinal cord at levels S2-S4; they terminate in the ganglionic cells located near or within the target organ
- both sympathetic and parasympathetic pre-ganglionic nerves release ACh which acts on a nicotinic receptor
- post-ganglionic sympathetic nerves release NE, which acts on alpha and beta receptors, while post-ganglionic parasympathetic nerves release ACh which acts on muscarinic receptors
- the exceptions are post-ganglionic sympathetic nerves to blood vessels, sweat glands, spleen capsule, adrenals, which do NOT have parasympathetic innervation

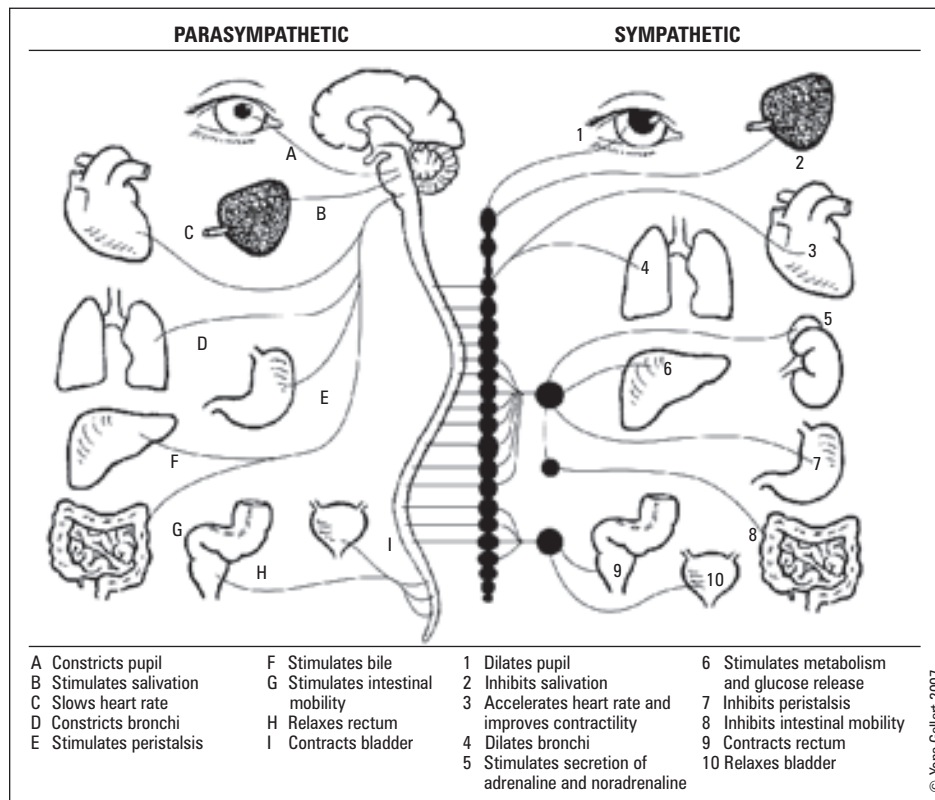


Figure 13. Autonomic Nervous System

Parasympathetic Nervous System (PNS)

- acetylcholine (ACh) is the main neurotransmitter of the parasympathetic nervous system
- ACh receptors include
 - nicotinic (pre-ganglionic) receptors located in the autonomic ganglia, and nicotinic (post-ganglionic) receptors in the adrenal medulla
 - muscarinic (only post-ganglionic) receptors
 - M_1 located in the CNS
 - M_2 receptors located on smooth muscle, cardiac muscle and glandular epithelium
- acetylcholine action is terminated by metabolism in the synaptic cleft by acetylcholinesterase and in the plasma by pseudocholinesterase
 - e.g. acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) are used to increase ACh levels in conditions such as myasthenia gravis and Alzheimer's disease

Sympathetic Nervous System (SNS)

- norepinephrine is the major neurotransmitter of the SNS
- receptors include
 - β_1 : predominately in cardiac tissue
 - β_2 : predominately in smooth muscle and glands
 - α_1 : predominately on post-synaptic receptors in smooth muscles and glands
 - α_2 : predominately on pre-synaptic terminals, where they feed back to inhibit further NE release; also exist as post-synaptic terminals in the brain, uterus and vascular smooth muscle
- norepinephrine action is terminated by reuptake by the presynaptic membrane, diffusion from the synaptic cleft and degradation by monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT)

Table 5. Direct Effects of Autonomic Innervation on the Cardiorespiratory System

Organ	Sympathetic Nervous System		Parasympathetic Nervous System	
	Receptor	Action	Receptor	Action
Heart				
1. Sinoatrial	β_1	Increased HR	M	Decreased HR
2. Atrioventricular Node	β_1	Increased conduction	M	Decreased conduction
3. Atria	β_1	Increased contractility	M	Decreased conduction
4. Ventricles	β_1	Increased contractility	M	Decreased conduction
Blood Vessels				
1. Skin, Splanchnic	α_1, α_2	Constriction	M	Dilatation
2. Skeletal Muscle	α	Constriction	M	Dilatation
	β_2 – large muscles	Dilatation	M	Dilatation
3. Coronary	α_1, α_2	Constriction	M	Dilatation
	β_2	Dilatation	M	Dilatation
Lungs				
1. Bronchiolar Smooth Muscle	β_2	Relaxation	M	Constriction
2. Bronchiolar Glands	α_1, β_2	Increased secretion	M	Stimulation

Opioid Analgesics

- in general, when converting from PO to IV, divide by a factor of 2
- when converting from one opioid to another, use 50-75% of the equivalent dose to allow for incomplete cross-tolerance
- rapid titration and prn use may be required to ensure effective analgesia for the first 24 hours
- dose equivalencies provided in the above table are approximate; individual patients vary
- opioids often used to manage mild to moderate pain include codeine, hydrocodone, and oxycodone
- moderate to severe pain is often managed using morphine, hydromorphone, oxycodone, fentanyl, methadone, or levorphanol

Table 6. Opioid Analgesics

Generic Name	Proprietary Name	Comments
Morphine	MS IR® ("immediate release" PO); MS Contin®, M-Eslon® (controlled release PO); various names for IV form	<ul style="list-style-type: none"> • Parenteral 10 mg morphine is usual standard for comparison • Morphine PO:IV = 60:10 for opioid naive patient, 30:10 for others • Do not crush, break, or chew oral controlled release morphine
Codeine	Tylenol® #1, #2, #3 Codeine Contin®, generics	<ul style="list-style-type: none"> • Metabolized to morphine by CYP2D6 (7-10% of Caucasians are non-metabolizers, due to polymorphisms) • Limited by potential toxicities of acetaminophen • No additional benefit at doses > 200 mg
Fentanyl	Sublimaze®	<ul style="list-style-type: none"> • Minimal experience outside the hospital setting
Fentanyl	Duragesic®	<ul style="list-style-type: none"> • Usually for stable pain, especially in patients with GI dysfunction • Transdermal 50 µg/h patch equivalent to 100 mg morphine PO/day
Hydromorphone	Vicodin®, Lortab®	<ul style="list-style-type: none"> • Limited by potential toxicities of acetaminophen or ibuprofen additive • Quick onset of action and thus highly addictive
Hydromorphone	Dilaudid®	<ul style="list-style-type: none"> • PO especially useful for initial dose titration and prn supplementation • IV form often used subcutaneously
Levorphanol	Levodromoran®	<ul style="list-style-type: none"> • Long half-life with relatively short dosing interval
Meperidine	Demerol®	<ul style="list-style-type: none"> • Not a 1st line opioid. May cause seizures due to the accumulation of normeperidine, its breakdown product • Avoid using > 48h, > 600 mg/24h and with MAOIs
Methadone	Dolophine®	<ul style="list-style-type: none"> • Long, variable half-life, which may complicate titration • Better used for withdrawal/abstinence therapy
Oxycodone	OxyContin® Oxy IR®, Endocodone® Percocet®, Percodan® (combination with ASA or acetaminophen)	<ul style="list-style-type: none"> • Often formulated in combination with acetaminophen/aspirin, use caution



When prescribing narcotics, remember **NBAL**:
 Narcotic (e.g. morphine 5 mg PO q4h)
 Breakthrough (e.g. morphine 2.5 mg PO q1h prn)
 Anti-emetic (e.g. metoclopramide 10 mg 30 min before each meal and qhs)
 Laxative (e.g. senokot PO qhs)



Equianalgesic Doses of Opioids		
Drug	PO Dose (mg)	IV Dose (mg)
Codeine	100	50
Morphine	10	3-5
Oxycodone	5	n/a
Hydromorphone	2	1
Hydrocodone	10	n/a

Titrating Opioid Analgesics with Continuous Opioid Infusion

- pain is most effectively managed using a combination of the basal/continuous rate plus PRN bolus/rescue/breakthrough doses
- at the initiation of the infusion, a loading dose of 2-5 times the hourly rate may be required for significant pain
- minimum 8 hours required for a new rate to reach steady state
 - basal/continuous rate should be increased no sooner than 8 hours after the last basal increase (ideally 24 hours between increases)
- use PRN doses – nurse administered or patient controlled analgesia (PCA) – to provide:
 - rapid response to the patient's need for pain relief between scheduled doses
 - a basis for future increases of the basal rate
- rescue/breakthrough doses are equal to 10% of the 24-hour rate, available q1h
- 24 hours after the last basal rate adjustment, calculate the total opioid dose in those 24 hours (basal rate + PRN doses); divide the total by 24 to reach the new hourly rate
- when the basal rate is increased, the rescue/breakthrough dose is changed proportionately to maintain that dose at 10% of the 24-hour dose

Common Drug Endings

Table 7. Common Drug Endings

Ending	Category	Example
-afil	Erectile dysfunction	sildenafil
-ane	Inhaled general anesthetic	halothane
-azepam	Benzodiazepine	lorazepam
-azole	Antifungal	ketoconazole
-olol	β -blocker	propanolol
-pril	ACE inhibitor	captopril
-terol	β_2 agonist	albuterol
-tidine	H ₂ agonist	cimetidine
-tropin	Pituitary hormone	somatotropin
-zosin	α_1 antagonist	prazosin

Note: Some medications are exceptions to the rule e.g. methimazole (antithyroid)

References

- Baker GR, Norton PG, Flintoft V et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. *CMAJ* 2004; 170:1678-86.
- Canadian Adverse Drug Reaction Monitoring Program (CADRMP) Adverse Reaction Database http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index_e.html
- Hardman JG and Limbird LR (eds) (1996). Goodman and Gilman's the Pharmacological Basis of Therapeutics (9th ed.). McGraw-Hill, New York.
- Hardy B, Bedard M (2002). Serum Drug Concentration Monitoring. In: Compendium of Pharmaceuticals and Specialties 2002. Repchinsky C (ed.). Canadian Pharmacists Association, Ottawa.
- Kalant H and Roschlau W (eds) (1999). Principles of Medical Pharmacology (6th ed.). Oxford University Press, New York.
- Katzung BG (ed) (2001). Basic and Clinical Pharmacology (8th ed.). McGraw-Hill Companies, New York.
- Lewis, T. (2004) Using the NO TEARS tool for medication review. *BMJ*. 329(7463):434.
- Rang H, Dale M, Ritter J (eds) (1999). Pharmacology (4th ed.). Churchill Livingstone, Edinburgh.
- Samoy LJ, Zed PJ, Wilbur K, et al. Drug-Related Hospitalizations in a Tertiary Care Internal Medicine Service of a Canadian Hospital: A Prospective Study. *Pharmacotherapy* 2006; 26(11): 1578-1586.

Notes_____

Venetia Lo, Farheen Mussani and Nancy Xi, chapter editors

Christopher Kitamura and Michelle Lam, associate editors

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Introduction to Skin

Skin Anatomy



Layers of the Epidermis
"Californians Like Getting Sun Burns"

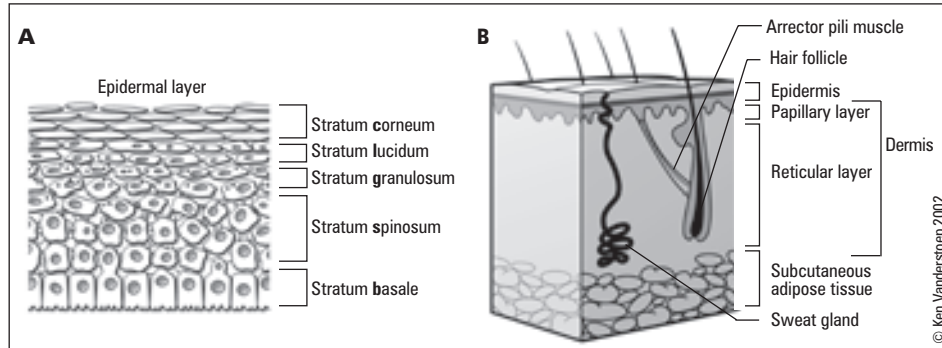


Figure 1. Cross-Section of the Various Layers of Skin. Epidermal layer is detailed in A

Skin

- divided anatomically into epidermis, dermis, and subcutaneous tissue
- epidermis**
 - avascular: receives its nutrition from the dermal capillaries
 - derived from keratinocytes with the youngest presenting at the 'base' (see layers Figure 1A)
 - cells progress from stratum basale to stratum corneum in about four weeks
 - stratum basale (germinativum): mitotic figures that give rise to keratinocytes
 - stratum spinosum (prickle cells): junctions in this layer (tonofilaments) give the epidermis its strength
 - stratum granulosum: flat cells containing basophilic granules which characterize skin
 - stratum lucidum: comprised of transparent layers of packed dead cells
 - stratum corneum: flat scales of the resistant protein keratin
 - other epidermal cells include melanocytes, Langerhans cells, and white blood cells
- dermis** – comprised of connective tissue divided into two regions:
 - papillary: contains numerous capillaries that supply nutrients to the dermis and epidermis
 - reticular: provides a strong structure for skin; consists of collagen bundles woven together along with elastic fibres, fibroblasts, and macrophages
- subcutaneous tissue** (subdermal)
 - consists primarily of adipose cells

Skin Appendages

- epidermal in origin; can extend into the dermis
- include hair, nails, and cutaneous glands

Cutaneous Glands

- sebaceous gland** – part of pilosebaceous unit, produces sebum which is secreted into the hair follicle via the sebaceous duct, where it covers the skin surface (protective function)
 - sebum has some antifungal properties
 - found over entire skin surface except palms and soles
- apocrine sweat gland** – apocrine duct empties into hair follicle above sebaceous gland
 - found in axillae and perineum
 - main function is to produce scent (i.e. pheromones)
- eccrine sweat gland** – not part of pilosebaceous unit
 - found over entire skin surface except lips, nail beds and glans penis
 - important in temperature regulation via secretion of sweat to cool skin surface

Skin Function

- protection
 - due to continuous recycling and avascularity of epidermis
 - barrier to: UV radiation, mechanical/chemical insults, pathogens and dehydration
- thermal regulation
 - insulation to maintain body temperature in cool environments, via hair and subcutaneous adipose tissue
 - dissipation of heat in warm environments, via increased activity of sweat glands and increased blood flow within dermal vascular networks
- sensation
 - largest sensory organ of the body, with touch, pain, and temperature sensation
- metabolic function
 - vitamin D synthesis
 - energy storage (mainly in the form of triglycerides)

Definitions

Primary Morphological Lesions

Definition

- an initial lesion that has not been altered by trauma or manipulation and has not regressed
- **macule**: flat lesion <1 cm
- **patch**: flat lesion ≥1 cm
- **papule**: elevated, palpable lesion <1 cm
- **plaque**: elevated, palpable lesion ≥1 cm
- **nodule**: deep, palpable lesion <1 cm, often dermal or subcutaneous in origin
- **tumour**: deep, palpable lesion ≥1 cm
- **vesicle**: fluid-filled lesion <1 cm
- **bulla**: fluid-filled lesion ≥1 cm
- **cyst**: a nodule containing semi-solid or fluid material
- **pustule**: an elevated lesion containing purulent fluid (white, grey, yellow, green)
- **erosion**: a disruption of the skin involving the epidermis alone, heals without scarring
- **ulcer**: a disruption of the skin that extends into the dermis or deeper; heals with scarring

Table 1. Types of Lesions

Profile	<1 cm Diameter	≥1 cm Diameter
Flat Lesion	Macule (e.g. freckle)	Patch (e.g. vitiligo)
Raised Superficial Lesion	Papule (e.g. wart)	Plaque (e.g. psoriasis)
Deep Palpable (dermal or subcutaneous)	Nodule (e.g. dermatofibroma)	Tumour (e.g. lipoma)
Elevated Fluid-filled Lesions	Vesicle (e.g. herpes simplex virus (HSV))	Bulla (e.g. bullous pemphigoid)

Secondary Morphological Lesions

Definition

- develop during the evolutionary process of skin disease, or created by manipulation, or due to complication of primary lesion (e.g. rubbing, scratching, infection)
- **crust**: dried fluid (serum, blood, or purulent exudate) originating from a lesion (e.g. impetigo)
- **scale**: excess keratin (e.g. seborrheic dermatitis)
- **lichenification**: thickening of the skin and accentuation of normal skin markings (e.g. chronic atopic dermatitis)
- **fissure**: a linear slit-like cleavage of the skin
- **excoriation**: a scratch mark
- **xerosis**: pathologic dryness of skin (xeroderma), conjunctiva (xerophthalmia), or mucous membranes
- **atrophy**: histological decrease in size and number of cells or tissues, resulting in thinning or depression of the skin

Other Morphological Lesions

- **comedones**: collection of sebum and keratin
 - open comedo (blackhead)
 - closed comedo (whitehead)
- **purpura**: extravasation of blood into dermis resulting in hemorrhagic lesions; non-blanchable
 - **petechiae**: small pinpoint purpura
 - **ecchymoses**: large flat purpura, "bruise"
- **telangiectasia**: dilated superficial blood vessels; blanchable
- **scar**: replacement fibrosis of dermis and subcutaneous tissue (hypertrophic or atrophic)
- **wheal**: a special form of papule or plaque that is blanchable and transient, formed by edema in the dermis (e.g. urticaria)



Describe a Lesion with SCALDA
Size and Surface area
Colour (e.g. hyperpigmented, hypopigmented, erythematous)
Arrangement (e.g. solitary, linear, reticulated, grouped, herpetiform)
Lesion morphology (see Table 1)
Distribution (e.g. dermatomal, intertriginous, symmetrical/asymmetrical, follicular)
Always check hair, nails, mucous membranes and intertriginous areas



Skin Phototypes (Fitzpatrick)

Phototype	Colour of Skin	Skin's Response to Sun Exposure (without SPF protection)
I	White	Always burns, never tans
II	White	Always burns, little tan
III	White	Slight burn, slow tan
IV	Pale brown	Slight burn, faster tan
V	Brown	Rarely burns, dark tan
VI	Dark brown or black	Never burns, dark tan

Patterns and Distribution

- **acral:** relating to the hands and feet (e.g. hand, foot and mouth disease)
- **annular lesions:** ring shaped (e.g. granuloma annulare)
- **follicular lesions:** involving hair follicles (e.g. folliculitis)
- **guttate lesions:** lesions following a “drop-like” pattern (e.g. guttate psoriasis)
- **Koebner phenomenon:** isomorphic response, appearance of lesions at an injury site (e.g. molluscum, lichen planus, psoriasis, warts)
- **morbilliform:** a maculopapular rash resembling measles
- **reticular lesions:** lesions following a net-like pattern (e.g. livedo reticularis)
- **satellite lesions:** lesions scattered outside of primary lesion (e.g. candida diaper dermatitis)
- **serpiginous lesions:** lesions following a snake-like pattern (e.g. cutaneous larva migrans)
- **target (iris) lesions:** concentric ring lesions, like a dartboard (e.g. erythema multiforme)
- **other descriptive terms:** discrete, clustered, linear, confluent, dermatitic, indurated

Differential Diagnoses of Common Presentations

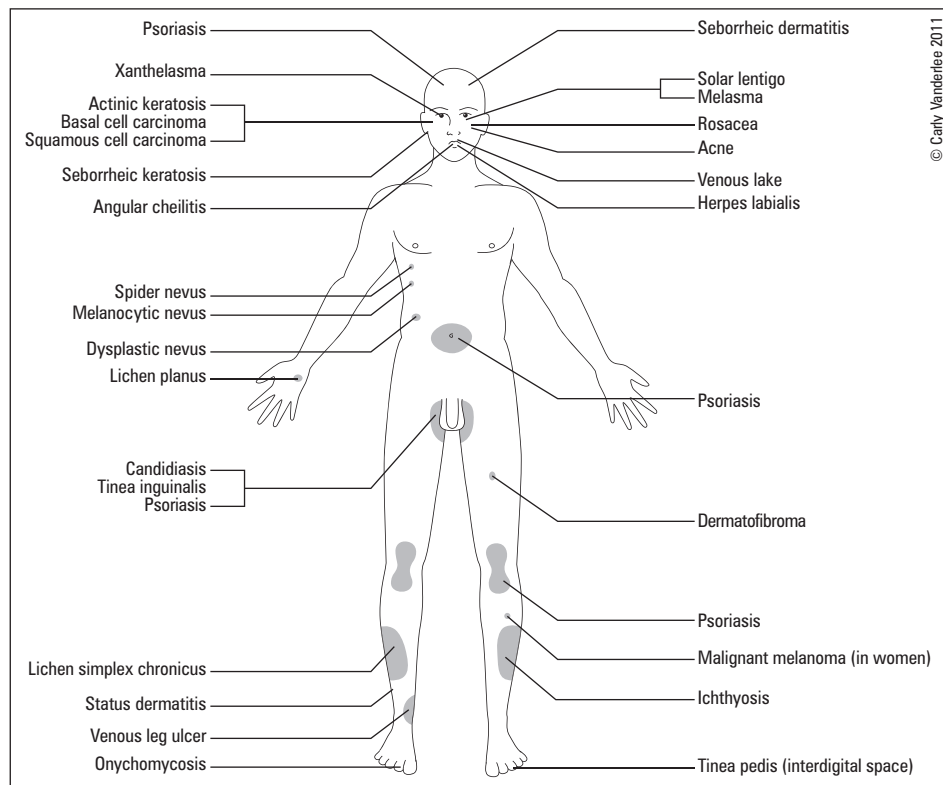


Figure 2. Common Lesions Based on Anatomical Distribution

Table 2. Differential Diagnosis of Common Presenting Problems

Lesion	Infectious	Inflammatory	Drug/Toxin	Miscellaneous
Brown Macule		Post-inflammatory hyper-pigmentation	UV radiation, actinic/solar lentigo, freckle (ephelide)	Congenital: café-au-lait spots, congenital nevus, epidermal/junctional nevus Neoplasia: lentigo maligna, malignant melanoma, pigmented basal cell carcinoma (BCC) Other: melasma/chloasma ("mask of pregnancy")
Discrete Red Papule	Folliculitis Furuncle Scabies	Acne vulgaris Lichen planus Rosacea Psoriasis Urticaria	Bites/stings	Vascular: hemangioma, pyogenic granuloma Other: dermatofibroma, miliaria rubra
Red Scales	Pityriasis rosea Secondary syphilis Tinea	Dermatitis (atopic, contact, nummular, seborrheic) Discoid lupus Lichen planus Psoriasis	Gold	Neoplastic: mycosis fungoides
Vesicle	Cat-Scratch disease Impetigo Viral: HSV, zoster, varicella, molluscum, coxsackie Scabies	Acute contact dermatitis Dyshidrotic eczema		Other: dermatitis herpetiformis, porphyria cutanea tarda
Bullae	Bullous impetigo	Acute dermatitis Erythema Multiforme (EM) Steven-Johnson Syndrome (SJS) Toxic Epidermal Necrosis (TEN) Systemic lupus erythematosus (SLE)	Fixed drug eruption	Autoimmune: bullous pemphigoid, pemphigus vulgaris Other: dermatitis herpetiformis, porphyria cutanea tarda
Pustule	Candida Dermatophyte Impetigo Sepsis Varicella	Acne vulgaris Rosacea Dyshidrotic dermatitis Pustular folliculitis Pustular psoriasis	Acute generalized exanthematous pustulosis (usually secondary to drug reaction)	Other: hidradenitis suppurativa
Oral Ulcer	Aspergillosis CMV Coxsackie Cryptococcosis HSV/HZV HIV, TB, Syphilis	Allergic stomatitis EM/SJS/TEN Lichen planus Seronegatives, SLE Recurrent aphthous stomatitis Behçet's disease	Chemotherapy Radiation therapy	Autoimmune: pemphigus vulgaris Congenital: XXY Hematologic: sickle cell disease Neoplasia: BCC, squamous cell carcinoma (SCC)
Skin Ulcer	Plague Syphilis TB Tularemia	RA, SLE, vasculitis Ulcerative colitis (pyoderma gangrenosum)		Autoimmune: necrobiosis lipoidica diabetorum (e.g. DM) Congenital: XXY Hematologic: sickle cell disease Neoplasia: SCC Vascular: arterial, neurotropic, pressure, venous, aphthous, leukoplakia, traumatic

Common Skin Lesions



Cysts

Table 3. Cysts

	Epidermal Cyst (Sebaceous)	Pilar Cyst (Trichilemmal)	Dermoid Cyst	Ganglion Cyst	Milium
Clinical Presentation	Round, yellow/flesh coloured, slow growing, mobile, firm, fluctuant, nodule or tumour	Multiple, hard, varying sized nodules under the scalp, lacks central punctum	Most commonly found at lateral third of eyebrow or midline under nose	Usually solitary, rubbery, translucent; a clear gelatinous viscous fluid may be extruded	1-2 mm superficial, white to yellow subepidermal papules occurring on eyelids, cheeks, and forehead Within pilosebaceous follicles
Pathophysiology	Epithelial cells displaced into dermis, epidermal lining becomes filled with keratin and lipid-rich debris May be post-traumatic	Thick walled cyst lined with stratified squamous epithelium and filled with dense keratin Idiopathic Post-trauma	Rare, congenital hamartomas, which arise from inclusion of epidermis along embryonal cleft closure lines, creating a thick walled cyst filled with dense keratin	Cystic lesion that originates from joint or tendon sheath, called a mucous cyst when found on fingertip Associated with osteoarthritis	Small epidermoid cyst, primarily arising from pluripotent cells in epidermal or adnexal epithelium Secondary to blistering, ulceration, trauma, topical corticosteroid atrophy, or cosmetic procedures
Epidemiology	Most common cutaneous cyst in youth – mid age	2 nd most common cutaneous cyst F>M	Rare	Older age	Any age 40-50% of infants
Clinical Course	Central punctum may rupture (foul, cheesy odour, creamy colour) and produce inflammatory reaction Increase in size and number over time, especially in pregnancy	Rupture causes pain and inflammation	If nasal midline, risk of extension into CNS	Stable	In newborns, spontaneously resolves in first 4 weeks of life
Management	Excise completely before it becomes infected	Excision	Excision	Drainage ± steroid injection if painful Compression daily for 6 weeks Excision if bothersome	Incision and expression of contents Laser ablation and electrodesiccation Multiple facial milia responds to topical retinoid therapy



Fibrous Lesions

DERMATOFIBROMA

Clinical Presentation

- button-like, firm dermal papule or nodule, skin-coloured to red-brown colouring
- majority are asymptomatic but may be pruritic and/or tender
- site: legs > arms > trunk
- dimple sign: lateral compression causes dimpling of the lesion

Pathophysiology

- benign tumour due to fibroblast proliferation in the dermis

Etiology

- unknown; often associated with history of minor trauma (e.g. shaving or insect bites)

Epidemiology

- adults, F>M

Differential Diagnosis

- dermatofibrosarcoma protuberans, malignant melanoma, Kaposi's sarcoma, blue nevus

Investigations

- biopsy if diagnosis is uncertain

Management

- no treatment required
- excision or cryosurgery if bothersome

SKIN TAGS**Clinical Presentation**

- small (1-10 mm), soft, skin-coloured or darker pedunculated papule, often polypoid
- sites: eyelids, neck, axillae, inframammary, and groin

Pathophysiology

- benign outgrowth of skin

Epidemiology

- middle-aged and elderly, F>M, obese

Differential Diagnosis

- pedunculated seborrheic keratosis, compound or dermal melanocytic nevus, neurofibroma

Management

- excision, electrodesiccation, cryosurgery

**Skin tags are also known as...**

- Acrochordons
- Fibroepithelial polyps
- Soft fibromas
- Pedunculated lipofibromas
- Cutaneous papillomas

Hyperkeratotic Lesions

SEBORRHEIC KERATOSIS**Clinical Presentation**

- well-demarcated waxy papule/plaque with classic “stuck on” appearance
- large variety in colour, size and shape
- over time lesions appear more warty, greasy and pigmented
- sites: face, trunk, upper extremities (may occur at any site except palms or soles)

Pathophysiology

- very common benign epithelial tumour

Epidemiology

- unusual <30 years old
- autosomal dominant inheritance

Differential Diagnosis

- malignant melanoma (lentigo maligna, nodular melanoma), melanocytic nevi, pigmented basal cell carcinoma, solar lentigo, spreading pigmented actinic keratosis

Investigations

- biopsy only if diagnosis uncertain

Management

- none required, for cosmetics only
- liquid nitrogen, curettage

ACTINIC KERATOSIS (SOLAR KERATOSIS)**Clinical Presentation**

- ill-defined, scaly erythematous papules or plaques on a background of sun damaged skin (solar heliosis)
- sandpaper-like, gritty sensation felt on palpation
- sites: areas of sun exposure (face, ears, scalp if bald, neck, sun exposed limbs)

Pathophysiology

- UV radiation damage to keratinocytes from repeated sun exposure (especially UVB)
- can develop into squamous cell carcinoma (1-10%)

**Types of Actinic Keratoses (AKs)**

- **Erythematous** – typical AK lesion
- **Hypertrophic** – thicker, rough papule/plaque
- **Cutaneous horn** – firm hyperkeratotic outgrowth
- **Actinic cheilitis** – confluent AKs on the lip
- **Pigmented** – flat, tan-brown, scaly plaque
- **Spreading pigmented**
- **Proliferative**
- **Conjunctival** – pinguecula, pterygium

Epidemiology

- common with increasing age, outdoor occupation, M>F
- skin phototypes I-III (see sidebar, D3), rare in darker skin as melanin is protective

Differential Diagnosis

- SCC in situ, superficial BCC, seborrheic keratosis, cutaneous lupus erythematosus

Investigations

- biopsy lesions that are refractory to treatment

Management

- destructive: liquid nitrogen, electrodesiccation and curettage
- pharmacotherapy: Efudex® (5-fluorouracil) cream for 2-3 weeks, Aldara® (imiquimod) cream for 8-10 weeks

**KERATOACANTHOMA****Clinical Presentation**

- rapid growing, firm, dome-shaped, erythematous or skin-coloured nodule with central keratin-filled crater, resembling an erupting volcano
- often spontaneously regresses within a year, leaving a scar
- sites: sun-exposed skin

Pathophysiology

- epithelial neoplasm with atypical keratinocytes in epidermis
- considered a low grade variant of SCC

Etiology

- HPV, UV radiation, chemical carcinogens (tar, mineral oil)

Epidemiology

- >50 years, rare <20 years

Differential Diagnosis

- treat as SCC until proven otherwise, hypertrophic solar keratosis, verruca vulgaris

Management

- surgical excision

CORNS**Clinical Presentation**

- firm papule with a central, translucent, cone-shaped, hard keratin core
- painful with direct pressure
- sites: most commonly on dorsolateral fifth toe and dorsal aspects of other toes

Pathophysiology

- localized hyperkeratosis induced by pressure on hands and feet

Epidemiology

- F>M, can be caused by wearing high-heeled shoes with a tapered toe

Differential Diagnosis

- tinea pedis, plantar warts

Management

- relieve pressure with padding or alternate footwear
- paring, curettage

**Corns vs. Warts vs. Callouses**

- Corns have a whitish yellow central translucent keratinous core. Painful with direct pressure.
- Warts bleed with paring and have a black speckled central appearance due to thrombosed capillaries. Plantar warts destroy dermatoglyphics (epidermal ridges).
- Callouses have layers of yellowish keratin revealed with paring. There are no thrombosed capillaries or interruption of epidermal ridges.

Keloids

Clinical Presentation

- firm, shiny, skin-coloured or red-bluish papules/nodules that most often arise from cutaneous injury (e.g. piercing, surgical scar, acne), but may appear spontaneously
- extends beyond the margins of the original injury, and may continue to expand in size for years with claw-like extensions
- can be pruritic and painful
- sites: earlobes, shoulders, sternum, scapular area

Pathophysiology

- excessive proliferation of randomly organized collagen fibers following trauma to skin
- differentiated from a hypertrophic scar which is confined to the borders of the original injury

Epidemiology

- predilection for darker skin
- M=F; all age groups

Management

- intralesional corticosteroid injections
- cryotherapy
- silicone compression



Keloids vs. Hypertrophic Scars

- **Keloids:** extend beyond margins of original injury with claw-like extensions
- **Hypertrophic scars:** confined to original margins of injury

Pigmented Lesions

Table 4. Comparison of Pigmented Lesions

	Ephelides (Freckles)	Solar Lentigo (Liver Spot)	Mongolian Spot	Becker's Nevus
Clinical Presentation	Small (<5 mm) well-demarcated light brown macules Sites: sun-exposed skin	Well demarcated brown/black irregular macules Sites: sun-exposed skin	Congenital grey-blue macule commonly on lumbosacral area	Hairy, light brown macule/patch with a papular verrucous surface Sites: trunk and shoulders
Pathophysiology	Increased melanin within basal layer keratinocytes secondary to sun exposure	Benign melanocytic proliferation in dermal-epidermal junction due to chronic sun exposure	Ectopic melanocytes in dermis	Pigmented hamartoma with increased melanin in basal cells
Epidemiology	Skin phototypes I and II	Most common in Caucasians > 40 years Skin phototype I-III	99% occurs in Asian and Aboriginal infants	M>F Often becomes noticeable at puberty
Differential Diagnosis	Junctional nevi Juvenile lentigines	Lentigo maligna, seborrheic keratosis, pigmented solar keratosis	Ecchymosis	Hairy congenital melanocytic nevus
Clinical Course and Management	No treatment required Multiply and darken with sun exposure, fade in winter Sunscreens may prevent the appearance of new freckles	Laser therapy, shave excisions, cryotherapy	Usually fades in early childhood but may persist into adulthood	Hair growth follows onset of pigmentation Cosmetic management (usually too large to remove)



DDx of Hyperpigmented Macules

- Purpura (e.g. solar, ASA, anti-coagulants, steroids, hemosiderin stain)
- Post-inflammatory
- Melasma
- Melanoma
- Fixed drug eruption

SEBORRHEIC KERATOSIS (see *Hyperkeratotic Lesions* section, D7)

NEVOMELANOCYTIC NEVI (NMN) (see Table 5)

- common mole
- be suspicious of new pigmented lesions in individuals >40 years
- average number of moles per person: 18-40
- 3 stages of evolution:
 - junctional NMN: macular; arise at dermal-epidermal junction
 - compound NMN: papular; nevus cells invade the papillary dermis
 - dermal NMN: skin coloured papules (no longer hyperpigmented); nevus cells completely migrate into dermis

Table 5. Nevomelanocytic Nevi Classification

Type	Age of Onset	Clinical Presentation	Histology	Management
Congenital NMN	Birth	Sharply demarcated pigmented brown plaque with regular/irregular contours \pm coarse hairs Rule out leptomeningeal involvement if on head/neck	Nevomelanocytes in epidermis (clusters) and dermis (strands)	Surgical excision if suspicious, due to increased risk of melanoma
Acquired NMN	Early childhood to age 40 Involute by age 60	Benign neoplasm of pigment-forming nevus cell Well circumscribed, round, uniformly pigmented macules/papules <1.5 cm Classified according to site of nevus cells		Excisional biopsy required if on scalp, soles, mucous membranes, anogenital area, or if varied colours, irregular borders, pruritic, bleeding, exposed to trauma
Junctional NMN	Childhood Majority progress to compound nevus	Flat, irregularly bordered, uniformly tan-dark brown, sharply demarcated smooth macule	Melanocytes at dermal-epidermal junction above basement membrane	Same as above
Compound NMN	Any age	Domed, regularly bordered, smooth, round, tan-dark brown papule Face, trunk, extremities, scalp NOT found on palms or soles	Melanocytes at dermal-epidermal junction; migration into dermis	Same as above
Dermal NMN	Adults	Soft, dome-shaped, skin-coloured to tan/brown papules or nodules, often with telangiectasia Sites: face, neck	Melanocytes exclusively in dermis	Same as above
Dysplastic NMN	Childhood	Variegated macule/papule with irregular indistinct melanocytes in the basal cell layer >6 mm Risk factors: positive family history	Hyperplasia and proliferation of melanocytes extending beyond dermal compartment of the nevus Often with region of adjacent nests	Follow q2-6 months with colour photographs for changes Excisional biopsy if lesion changing or highly atypical
Halo NMN	First 3 decades	Brown oval/round papules surrounded by hypomelanosis Same sites as nevocellular nevus Spontaneous involution with regression of centrally located pigmented nevus	Dermal or compound nevocellular nevus surrounded by hypomelanosis, lymphocytes, histocytes	None required Excision if colour variegated or irregular borders Associated with vitiligo, metastatic melanoma
Blue NMN	Childhood and late adolescence	Uniformly blue to blue-black macule/papule with smooth border <6 mm	Pigmented melanocytes and melanophages in dermis	Remove if sudden onset or has changed



Vascular Lesions

Table 6. Vascular Tumours Compared to Vascular Malformations

	Vascular Tumours	Vascular Malformations
Definition	Endothelial hyperplasia	Normal endothelial turnover
Presence at Birth	Usually postnatal	100% at birth (not always obvious)
M:F	1:3-1:5	1:1
Natural History	Phases: • Proliferating • Involuting • Involved	Proportionate growth (can expand)

HEMANGIOMAS

Clinical Presentation

- is a vascular tumour, defines as benign proliferation of vessels in the dermis
- is red or blue, nodular and blanches with pressure
- includes: cavernous hemangioma, capillary/infantile hemangioma, spider hemangioma

Table 7. Vascular Tumours

	Hemangioma	Capillary/Infantile (spider strawberry nevus)	Spider Angioma (Campbell telangiectasia)	Cherry Angioma (Demorgan spot)	Pyogenic Granuloma
Clinical Presentation	Soft, compressible, bluish, subcutaneous mass that feels like a bag of worms when palpated Site: anywhere (distribution may indicate underlying cranial abnormality)	Congenital red/blue nodules	Central red arteriole with slender branches, faintly pulsatile, blanchable Sites: face, forearms, and hands	Bright red to deep maroon, dome-shaped vascular papules, 1-5 mm Site: trunk Less friable compared to pyogenic granulomas	Bright red, dome-shaped sessile or pedunculated nodule Sites: fingers, lips, mouth, trunk, toes DDx: glomus tumour, nodular malignant melanoma, SCC, nodular BCC
Pathophysiology	Deeply situated proliferation of thick-walled blood vessels	Congenital benign vascular proliferation of endothelial lining (consumptive thrombocytopenia if hemangioma enlarges rapidly) Can be part of PHACES syndrome	Associated with hyperestrogenic state (e.g. in hepatocellular disease, pregnancy, oral contraceptive pill)	Benign vascular neoplasm	Rapidly developing hemangioma Proliferation of capillaries with erosion of epidermis and neutrophilia
Epidemiology	Can be congenital Most appear later			>30 years old	<30 years old
Clinical Course	Can ulcerate Persists, generally do not involute	Appears shortly after 9 months, increases in size over months, then regresses 50% of lesions resolve spontaneously by 5 years	Increase in number over time	Lesions bleed frequently and persist for months	
Management	Surgical removal	Consider excision if not gone by school age. 10% require treatment due to functional impairment (visual compromise, airway obstruction, high output cardiac failure) or cosmesis Propranolol; systemic corticosteroids	Electro or laser surgery Systemic corticosteroids and INF- α may be indicated for rapidly growing lesions	Usually no treatment needed Laser or electrocautery for small lesions Excision of large lesions if necessary	Surgical excision with histologic examination Electrocautery; laser; cryotherapy



A spider angioma will blanch when the tip of a paperclip is applied to the centre of the lesion.



Pyogenic Granuloma is a misnomer: it is neither pyogenic nor granulomatous.

VASCULAR MALFORMATIONS

1. Nevus flammeus (Port-wine stain)

Clinical Presentation

- red to blue macule present at birth that follows a dermatomal distribution, rarely crosses midline
- most common site: nape of neck

Pathophysiology

- congenital vascular malformation of dermal capillaries; associated with Sturge Weber syndrome (V1, V2 distribution)

Management

- laser or camouflage (i.e. make-up)

2. Nevus simplex (salmon patch)

Clinical Presentation

- pink-red irregular patches
- midline macule on glabella known as "Angel Kiss"; on nuchal region known as "Stork Bites"
- present in 1/3 of newborns
- majority regress spontaneously

Pathophysiology

- congenital dilation of dermal capillaries

Management

- no treatment required

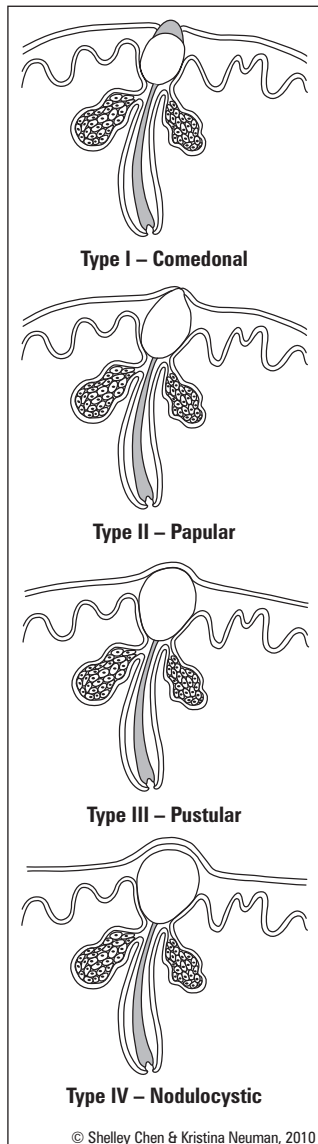


Figure 3. Types of Acne

**Acne Myths Debunked**

- Eating greasy food and chocolate does not cause or worsen acne
- Blackheads (comedones) are black because of oxidized melanin, not dirt

**Acne Exacerbating Factors**

- Systemic medications: lithium, phenytoin, steroids, halogens, androgens, iodides, bromides, danazol
- Topical agents: steroids, tars, ointments, oily cosmetics
- Mechanical pressure or occlusion, such as leaning face on hands
- Emotional stress

Acneiform Eruptions

Acne Vulgaris/Common Acne

Clinical Presentation

- a common inflammatory pilosebaceous disease categorized with respect to severity
 - Type I – **comedonal**, sparse, no scarring
 - Type II – comedonal, **papular**, moderate \pm little scarring
 - Type III – comedonal, papular, and **pustular**, with scarring
 - Type IV – **nodulocystic** acne, risk of severe scarring
- predilection sites: face, neck, upper chest, and back

Pathogenesis

- follicular hyperkeratinization blocks the secretion of sebum (comedones)
- androgens stimulate sebaceous glands to produce sebum
- anaerobic diphtheroid *Propionibacterium acnes* bacteria contains lipase, which converts sebum to free fatty acids and produces pro-inflammatory mediators

Epidemiology

- age of onset in puberty (10-17 years in females, 14-19 years in males)
- more severe in males than in females
- incidence decreases in adulthood
- genetic predisposition: majority of individuals with cystic acne have parent(s) with history of severe acne

Differential Diagnosis

- folliculitis, keratosis pilaris (upper arms, face, thighs), perioral dermatitis, rosacea

Management

- see Table 8

Table 8. Acne Treatments and Mechanisms of Action

Drug Name	Mechanism of Action	Notes
MILD ACNE: Topical Therapies		
clindamycin phosphate (e.g. Dalacin T®)	Lincosamide antibiotic; inhibits protein synthesis	Generally regarded as unsafe in lactation
erythromycin	Macrolide antibiotic; inhibits protein synthesis	Local skin reactions include burning, peeling, dryness, pruritus, erythema
benzoyl peroxide	Protein oxidant with bactericidal effect	Dry skin, contact dermatitis Apply to the point of dryness and erythema, but not discomfort
BenzaClin® gel	1% clindamycin and 5% benzoyl peroxide	See above
erythromycin + benzoyl peroxide (Benzamycin®)	3% erythromycin and 5% benzoyl peroxide	See above
adapalene (e.g. Differin®)	Comedolytic	Less irritating than tretinoin. No interaction with sun
tretinoin (e.g. Retin-A®)	Comedolytic	Sun sensitivity and irritation
MODERATE ACNE: After topical treatments have failed, add oral antibiotics, such as tetracycline (500 mg PO daily to bid), or erythromycin (500 mg PO bid). Antibiotics require 3-6 months of use before assessing efficacy. Consider hormonal therapy, including antiandrogens		
tetracycline	Systemic antibiotic	Use caution with regard to drug interactions: do not use with isotretinoin
cyproterone acetate-ethinyl estradiol (Diane-35®)	Cyproterone: potent anti-androgenic, progestogenic and antigonadotrophic activity Ethinyl estradiol: increases level of sex hormone binding globulin (SHBG), reducing circulating plasma levels of androgens	After 35 years of age, estrogen/progesterone should only be considered in exceptional circumstances, carefully weighing the risk/benefit ratio with physician guidance

Table 8. Acne Treatments and Mechanisms of Action (continued)

Drug Name	Mechanism of Action	Notes
SEVERE ACNE: Consider systemic retinoids after above treatments have failed		
isotretinoin (Accutane®, Clarus®)	Retinoid that inhibits sebaceous gland function and regulates keratinization	Teratogenic: contraindicated during pregnancy, unsafe in lactation; reliable contraception is necessary Signed informed consent is needed when prescribing Baseline lipid profile, hepatic enzymes and β -hCG before treatment May transiently exacerbate acne May cause depression Drug may be discontinued at 16-20 weeks when nodule count has dropped by >70% A second course may be initiated after 2 months prn Refractory cases may require 3 or more courses of isotretinoin

**Isotretinoin and Lipids**

Case reports indicate isotretinoin-induced hypertriglyceridemia can be successfully controlled with concurrent hypolipidemic therapy.

Perioral Dermatitis

Clinical Presentation

- discrete erythematous micropapules that often become confluent, forming inflammatory plaques on perioral and periorbital skin
- commonly symmetrical, rim of sparing around vermilion border of lips
- aggravated by topical glucocorticoids

Epidemiology

- 15-40 years old
- predominantly females

Differential Diagnosis

- dermatitis, rosacea, acne vulgaris

Management

- topical: metronidazole 0.75% gel or 0.75-1% cream to area BID
- systemic: tetracycline

Rosacea

Clinical Presentation

- chronic acneiform, inflammatory skin disease
- flushing (transient erythema) with a burning sensation is common initially, however non-transient erythema is the commonest sign of rosacea
- dome-shaped red papules \pm pustules, contributing to a florid, ruddy complexion
- differentiated from acne by the absence of comedones
- sites typically affected: convexities of the central face (forehead, nose, cheeks and chin)
 - may also affect the scalp, neck, and the upper part of body
- characterized by remissions and exacerbations
- all forms of rosacea can progress from mild to moderate to severe
- in longstanding rosacea, signs of thickening, induration, lymphedema in the skin
- phyma: a distinct swelling caused by lymphedema and hypertrophy of subcutaneous tissue, particularly affecting the nose (rhinophyma)
- ocular manifestations: conjunctivitis, keratitis, iritis
- exacerbating factors: heat, cold, wind, sun, stress, drinking hot liquids, alcohol, caffeine, spices (triggers of vasodilatation)

Pathophysiology

- unknown

Epidemiology

- although found in all skin types, highest prevalence in fair-skinned people
- 30-50 years old
- F>M

**Guidelines for the Diagnosis of Rosacea**

Presence of one or more of the following primary features:

- Flushing (transient erythema)
- Nontransient erythema
- Papules and pustules
- Telangiectasia

May include one or more of the following secondary features:

- Burning or stinging
- Plaque
- Dry appearance
- Edema
- Phymatous changes
- Ocular manifestations
- Peripheral location



Subtypes and Variants of Rosacea and Their Characteristics

SUBTYPE

Erythematotelangiectatic

Flushing, persistent central facial erythema ± telangiectasia

Papulopustular

Persistent central facial erythema
Transient central facial papules or pustules or both

Phymatous

Thickening skin, irregular surface nodularities and enlargement
Nose, chin, forehead, cheeks or ears

Ocular

Foreign body sensation in the eye, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periorbital edema

VARIANT

Granulomatous

Noninflammatory, hard, brown, yellow, or red cutaneous papules or nodules of uniform size

Management

- avoid topical corticosteroids
- cosmetic camouflage
- telangiectasia: treated by physical ablation; electrical hyfrecators, vascular lasers, and intense pulsed light therapies
- phymas: treated by physical ablation or removal; paring, electrosurgery, cryotherapy, laser therapy [CO₂, argon, neodymium-doped yttrium aluminum garnet (Nd:YAG)]
- early diagnosis and prompt treatment are recommended to prevent worsening

Table 9. Specific Rosacea Treatments

1st Line	2nd Line	3rd Line
Oral tetracyclines (250-500 mg PO bid)	Topical clindamycin	Oral retinoids
Topical metronidazole	Topical erythromycin 2% solution	Topical sulfur
Oral erythromycin (250-500 mg PO bid)	Topical benzoyl peroxide	
	Oral metronidazole	
	Ampicillin	

Dermatitis (Eczema)

Definition

- inflammation of the skin

Clinical Presentation

- symptoms include pruritus and pain
- acute dermatitis: papules, vesicles
- subacute dermatitis: scaling, crusting
- chronic dermatitis: lichenification, xerosis, fissuring

Asteatotic Dermatitis

Clinical Presentation

- diffuse, mild pruritic dermatitis secondary to dry skin
- very common in elderly, especially in the winter (a.k.a. “winter itch”) but starts in the fall

Management

- skin rehydration with moisturizing routine
- ± mild corticosteroid creams

Atopic Dermatitis

Clinical Presentation

- subacute and chronic eczematous reaction associated with prolonged severe pruritus
- distribution
 - infant (onset at 2-6 months old): face, scalp, extensor surfaces
 - childhood (>18 months): flexural surfaces
 - adult: hands, feet, flexures, wrists, face, forehead, eyelids, neck
- inflammation, lichenification, excoriations are secondary to relentless scratching
- atopic palms: prominent palmar creases
- associated with
 - keratosis pilaris (hyperkeratosis of hair follicles, “chicken skin”)
 - xerosis
 - occupational hand dryness

Epidemiology

- frequently affects infants, children, and young adults
- females only slightly more at risk than males (1.3:1 over the age of 2 years)
- almost 15% of children in developed countries under the age of 5 are affected; half of these cases are diagnosed by 1 year of age
- associated with personal or family history of atopy (asthma, hay fever, anaphylaxis, eosinophilia)
- polygenic inheritance: one parent >60% chance for child; two parents >80% chance for child
- childhood onset and hereditary forms may be associated with a defect in the protein filaggrin
- the earlier the onset, the more severe and persistent the disease
- long-term condition with 1/3 of patients continuing to show signs of AD into adulthood

Pathophysiology

- Th2 cellular response

Investigations

- no gold standard for diagnosis
- consider: skin biopsy, immunoglobulin serum levels (often elevated serum IgE level), patch testing, and skin prick tests



Triggers for Atopic Dermatitis

- Irritants (detergents, solvents, clothing, water hardness)
- Contact allergens
- Environmental aeroallergens (dust mites)
- Inappropriate bathing habits (long hot showers)
- Sweating
- Microbes (*S. aureus*)
- Stress

Management

- goal: reduce signs and symptoms, prevent or reduce recurrences/flares
- better outcome (e.g. less flare-ups, modified course of disease) if diagnosis made early and treatment plan individualized
 - individualized based on age, severity, sites and extent of involvement, presence of infection, previous responses to therapy
- avoid triggers of AD
- **enhance barrier function of the skin**
 - regular application of moisturizers
 - emollients hydrate the skin and reduce pruritus
 - twice daily application is recommended even in absence of symptoms, especially after bathing or swimming
 - bathing promotes hydration when followed by the application of moisturizers to the skin
- **anti-inflammatory therapies**
 - topical corticosteroids
 - effective, rapid symptomatic relief of acute flares
 - best applied immediately after bathing
 - control inflammation with a potent topical steroid; a milder one following resolution of acute flare
 - systemic immunosuppression may be needed in severe cases
 - flares may respond to systemic anti-staphylococcal therapy
 - side effects: skin atrophy, purpura, striae, steroid acne, perioral dermatitis, and glaucoma when used around the eyes
 - topical immunomodulators
 - long-term management
 - calcineurin inhibitors include pimecrolimus (Elidel®), tacrolimus (Protopic®)
 - side effects: skin burning, transient irritation
 - advantages of immunomodulators over long-term corticosteroid use
 - ♦ rapid, sustained effect in controlling pruritus
 - ♦ no skin atrophy
 - ♦ safe for the face and neck

Complications

- infections
 - treatment of infections
 - ♦ topical mupirocin or fusidic acid
 - ♦ oral antibiotics (e.g. cloxacillin, cephalexin) for widespread *S. aureus* infections

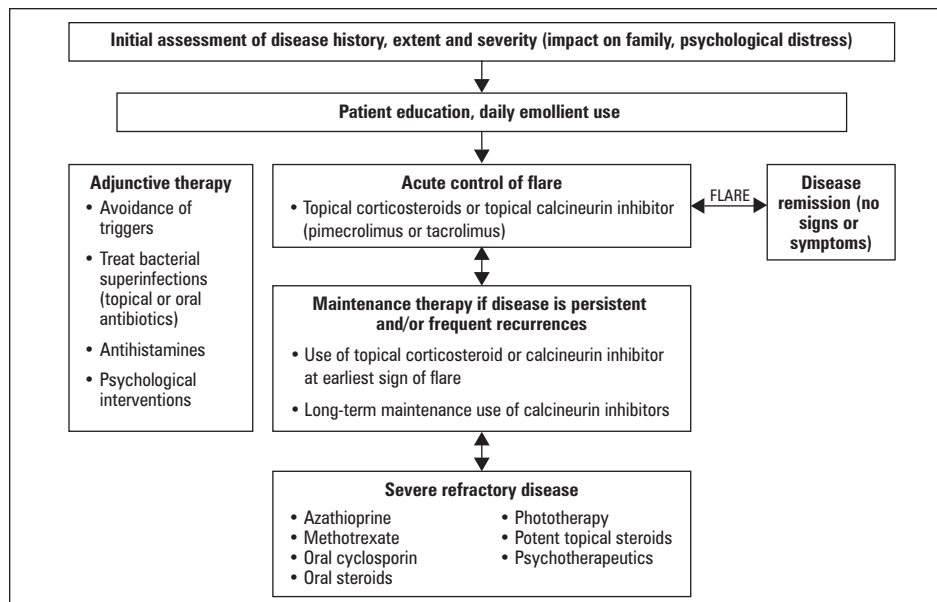


Figure 4. Atopic Dermatitis Treatment Algorithm

Adapted from: Ellis C, et al. ICCAD II Faculty. International Consensus Conference on Atopic Dermatitis II (ICCAD II): clinical update and current treatment strategies. *Br J Dermatol.* 2003; 148 (Suppl 63):3-10.



Contact Dermatitis

Top Ten Allergens as Identified by The North American Contact Dermatitis Group

Test Substance	Allergic Reactions (%)	Common Uses
Nickel sulfate	14.2	Found in some jewelry, buckles
Neomycin sulfate	13.1	Most commonly used topical antibiotic
Balsam of Peru	11.8	Fragrance material
Fragrance mix	11.7	A mix of eight different fragrance components which was developed to allow for allergen testing in cosmetics
Thimerosal	10.9	A common preservative that is used in vaccines, contact lens solution, cosmetics
Sodium gold	9.5	Used in jewellery, dentistry, thiosulfate electronics
Formaldehyde	9.3	A colourless gas found in many workplaces, cosmetics, medications, textiles, resins, plastic bottles
Quaternium-15	9.0	A component in many shampoos, moisturizers, conditioners and soaps
Cobalt chloride	9.0	A hard metal found in cosmetics, jewellery, buttons, tools
Bacitracin	8.7	A topical antibiotic

Clinical Presentation

- cutaneous inflammation from the interaction between external agent(s) and the skin

Table 10. Contact Dermatitis

	Irritant Contact Dermatitis	Allergic Contact Dermatitis
Mechanism of Reaction	Toxic injury to skin; non-immune mechanism	Cell-mediated delayed (Type IV) hypersensitivity reaction
Type of Reaction	Erythema, dryness, fine scale, burning Acute: quick reaction, sharp margins (e.g. from acid/alkali exposure) Cumulative insult: slow to appear, poorly defined margins (e.g. from soap), more common	Erythema with a papulovesicular eruption, swelling, pruritus
Frequency of Contact Dermatitis	Majority; will occur in anyone given sufficient concentration of irritants	Minority; patient acquires susceptibility to allergen that persists indefinitely
Distribution	Palmar surface of hand usually involved	Dorsum of hand usually involved; often discrete area of skin involvement
Examples	Soaps, weak alkali, detergents, organic solvents, alcohol, oils	(See sidebar) Many allergens are irritants, so may coincide with irritant dermatitis
Management	Avoidance of irritants Wet compresses with Burow's solution Barrier moisturizers Topical/oral steroids	Patch testing to determine specific allergen Avoid allergen and its cross-reactants Wet compresses soaked in Burow's solution (drying agent) Steroid cream (hydrocortisone 1%, betamethasone valerate 0.05% or 0.1% cream; bid) Systemic steroids prn (prednisone 1mg/kg, taper over 2 weeks)

Dyshidrotic Dermatitis

Clinical Presentation

- "tapioca pudding" papulovesicular dermatitis of hands and feet that coalesce into plaques, followed by painful fissuring
- acute stage often very pruritic
- secondary infection common
- lesions heal with desquamation and may lead to chronic lichenification
- sites: palms and soles ± dorsal surfaces of hands and feet

Pathophysiology

- NOT caused by hyperhidrosis (excessive sweating)
- emotional stress may precipitate the dermatitis

Management

- topical: high potency corticosteroid with plastic cling wrap occlusion to increase penetration
- intralesional triamcinolone
- systemic:
 - prednisone in severe cases
 - antibiotics for secondary *S. aureus* infection

Nummular Dermatitis

Clinical Presentation

- annular, coin-shaped, pruritic, erythematous plaques, dry, scaly, lichenified
- often associated with atopic and dyshidrotic dermatitis
- secondary infection common

Management

- moisturization
- corticosteroid ointment BID

Seborrheic Dermatitis

Clinical Presentation

- greasy, erythematous, yellow, scaling papules and plaques in areas rich in sebaceous glands
- infants: one cause of “cradle cap”
- children: may be generalized with flexural and scalp involvement
- adults: diffuse involvement of scalp margin with yellow to white flakes, pruritus, and underlying erythema
- sites: scalp, eyebrows, eyelashes, beard, glabella, post-auricular, over sternum, trunk, body folds, genitalia

Pathophysiology

- possible etiologic association with *Pityrosporum ovale* (yeast)

Epidemiology

- common in infants and at puberty
- increased incidence in immunocompromised patients (e.g. HIV)
- in adults, can cause dandruff (pityriasis sicca)

Management

- face: Nizoral® cream OD + mild steroid cream OD or BID
- scalp: salicylic acid in olive oil or Derma-Smoother FS® lotion (peanut oil, mineral oil, fluocinolone acetonide 0.01%) to remove dense scales, 2% ketoconazole shampoo (Nizoral®), ciclopirox (Stieprox®) shampoo, selenium sulfide (e.g. Selsun®) or zinc pyrithione (e.g. Head and Shoulders®) shampoo, steroid lotion (e.g. betamethasone valerate 0.1% lotion bid)

Stasis Dermatitis

Clinical Presentation

- persistent skin inflammation of the lower legs with brown pigmentation, erythema, xerosis, and scaling
- associated with venous insufficiency

Management

- support stockings
- rest and elevate legs
- moisturizer to treat xerosis
- mild topical corticosteroids to control inflammation

Complications

- ulceration (common in medial malleolus), secondary bacterial infections

Lichen Simplex Chronicus

Clinical Presentation

- chronic dermatitis resulting from continued rubbing/scratching of skin
- may develop secondarily to another pruritic skin disease
- lichenified (thickened) skin

Management

- treat pruritus to break the itch-scratch cycle: antihistamines, topical antipruritics
- topical corticosteroids (extremely potent)

Papulosquamous Diseases

Lichen Planus

Clinical Presentation

- acute or chronic inflammation of mucous membranes or skin characterized by violaceous papules, especially on flexural surfaces
- small, polygonal, flat-topped, shiny, violet papules; resolves into hyperpigmented macules
- sites: wrists, ankles, mucous membranes in 60% (mouth, vulva, glans), nails, scalp
- Wickham's striae: greyish lines over surface; pathognomonic
- mucous membrane lesions: lacy, whitish reticular network, milky-white plaques/papules; increased risk of SCC in erosions and ulcers
- nails: longitudinal ridging; dystrophic
- scalp: scarring alopecia
- spontaneously resolves in weeks or lasts for years (mouth and shin lesions)
- Koebner phenomenon "isomorphic reaction": develops in areas of trauma

Epidemiology

- association with hepatitis C
- may be triggered by severe emotional stress

Management

- topical corticosteroids with occlusion or intradermal steroid injections
- short courses of oral prednisone (rarely)
- photochemotherapy for generalized or resistant cases
- oral retinoids for erosive lichen planus in mouth

Pityriasis Rosea

Clinical Presentation

- acute, self-limiting, erythematous eruption characterized by red, oval plaques/patches with central scales that do not extend to edge of lesion
- long axis of lesions follows parallel to ribs producing "Christmas tree" pattern on back
- varied degree of pruritus
- most start with a "Herald" patch which precedes other lesions by 1-2 weeks
- sites: trunk, proximal aspects of arms and legs

Etiology

- suspected human herpes virus 7

Management

- none required; clears spontaneously in 6-12 weeks, reassurance
- topical corticosteroids when post-inflammatory pigmentation is a concern

Psoriasis

Classification

1. plaque psoriasis
2. guttate psoriasis
3. erythrodermic psoriasis
4. pustular psoriasis
5. psoriatic arthritis

Differential Diagnosis

- atopic dermatitis, mycosis fungoides (cutaneous T-cell lymphoma), seborrheic dermatitis, tinea

Diagnosis

- often clinical, biopsy to confirm
- PASI (Psoriasis Area and Severity Index)
 - score is based on: percentage of surface area involved and the severity of symptoms (erythema, infiltration, desquamation)



The 6 P's of Lichen Planus

Purple, Pruritic, Polygonal, Peripheral, Papules, Penis (i.e. mucosa)



PSORIASIS: Presentation and Pathophysiology

Pink papules/Plaques/Pinpoint bleeding (Auspitz sign)/Physical injury (Koebner phenomenon)

Silver scale/Sharp margins

Onycholysis/Oil spots

Rete Ridges with Regular elongation

Itching

Arthritis/Abscess (Munro)/Autoimmune

Stratum corneum with nuclei

Immunologic

Stratum granulosum absent

1. PLAQUE PSORIASIS

Clinical Presentation

- chronic and recurrent disease characterized by well-circumscribed erythematous papules/plaques with silvery-white scales
- worse in winter (lack of sun and humidity)
- Koebner phenomenon "isomorphic response": induction of new lesion by injury
- Auspitz sign: bleeds from minute points when scale is removed
- usually non-pruritic
- exacerbating factors: drugs (lithium, ethanol, chloroquine, beta-blockers), stress
- sites: scalp, extensor surfaces of elbows and knees, trunk, nails, pressure areas

Pathophysiology

- decreased epidermal transit time from stratum basale to stratum corneum
- shortened cell cycle of psoriatic compared to normal skin
- TH1-mediated inflammatory response

Management

- preventative measures
 - avoid sunburns
 - avoid drugs that exacerbate the condition (e.g. beta-blockers, lithium, corticosteroid rebound phenomenon, interferon)
- first-line treatment
 - mainly topical, usually prescribed if less than 5-10% of total body surface area is involved
 - first-line topical treatments include moderate to potent steroids, vitamin D analogues, retinoids, anthralin, coal tar, salicylic acid
 - if the affected area is >10%, use topical medications as adjuncts to phototherapy or systemic drugs
- second-line treatment
 - include cyclosporin, methotrexate, acitretin, phototherapy
- third-line treatment
 - biologics including alefacept, etanercept, infliximab, adalimumab, ustekinumab
- systemic treatments should be considered if:
 - psoriatic lesions cover >10% of total body surface area
 - unsuccessful topical therapies
 - psychological distress

Table 11. Topical Treatment of Psoriasis

Treatment	Mechanism	Comments
Lubricants	Reduce fissure formation	Petrolatum is effective
Salicylic acid 1-12%	Remove scales	
Tar (LCD: Liquor carbonis detergens) 20% coal tar solution	Inhibits DNA synthesis, increases cell turnover	Poor long term compliance
Calcipotriene (Dovonex [®] , Dovobet [®])	Binds to skin 1,25-dihydroxyvitamin D3 to inhibit keratinocyte proliferation	Not to be used on face or skin folds
Corticosteroid ointment	Reduce scaling and thickness	Use appropriate potency steroid in different areas for degree of psoriasis
Tazarotene (Tazorac [®]) (gel/cream)	Retinoid derivative	Use on nails

Table 12. Systemic Treatment of Psoriasis

Treatment	Adverse Effects
Methotrexate	Bone marrow toxicity, hepatic cirrhosis
Psoralens and long wave ultraviolet radiation (PUVA)	Pruritus, burning, cataracts, skin cancer
Acitretin	Alopecia, cheilitis, teratogenicity, epistaxis, xerosis, hypertriglyceridemia
Cyclosporine	Renal toxicity, hypertension, immunosuppression
UVB and "Narrow band" UVB (311-312 nm)	Well tolerated

Table 13. "Biologics" approved in Canada

Treatment	Route	Dosing Schedule	Effectiveness	Action
alefacept (Amevive [®])	IM	Weekly	+	T-cell
etanercept (Enbrel [®])*	SC	Twice weekly initially	+++	TNF
adalimumab (Humira [®])*	SC	Once every 2 weeks	++++	TNF
infliximab (Remicade [®])*	IV	~Every 2 months	+++++	TNF
ustekinumab (Stelara [®])	SC	Every 12 weeks during maintenance	++++	IL 12/23

*Can also be used to treat psoriatic arthritis



PSORIASIS: Triggers

Physical trauma (Koebner's phenomenon)
Infections (acute streptococcal infection precipitates guttate psoriasis)
Stress (can be a major factor in flares)
Drugs (systemic glucocorticoids, oral lithium, antimalarial drugs, interferon)
Alcohol ingestion

Topical Treatments for Chronic Plaque Psoriasis

Cochrane Database of Systematic Reviews 2009, Issue 2

Study: Systematic review of randomized trials comparing treatments against placebo or against vitamin D.

Patients: 21,448 patients with chronic plaque psoriasis.

Intervention: Corticosteroids, dithranol, tarazotene, salicylic acid, retinoids, methotrexate, macrolactams, vitamin D, and vitamin D + corticosteroids.

Outcome: Investigator assessment of overall global improvement. Total severity scores. Psoriasis area and severity index. Patient assessment of overall global improvement.

Results: Corticosteroids, vitamin D, dithranol, and tarazotene performed better than placebo alone. A combination of corticosteroids and vitamin D were better than either vitamin D or corticosteroids alone.



Calcipotriol is a vitamin D derivative

Dovobet[®] = calcipotriene combined with betamethasone dipropionate and is considered to be the most potent topical psoriatic therapy.



Mechanism of Biologics

"-mab" = monoclonal antibody
"-cept" = receptor

2. GUTTATE PSORIASIS ("DROP-LIKE")

Clinical Presentation

- discrete, scattered salmon-pink scaling papules
- sites: generalized, sparing palms and soles
- often antecedent streptococcal pharyngitis

Management

- UVB phototherapy, sunlight, lubricants
- penicillin V or erythromycin if Group A beta-hemolytic *Streptococcus* on throat culture

3. ERYTHRODERMIC PSORIASIS

Clinical Presentation

- generalized erythema with fine desquamative scale on surface
- associated symptoms: arthralgia, severe pruritus
- may present in patient with previous mild plaque psoriasis
- aggravating factors: lithium, beta-blockers, NSAIDs, antimalarials, phototoxic reaction, infection

Management

- hospitalization, bedrest, IV fluids, monitor fluid and electrolytes
- treat underlying aggravating condition, sun avoidance
- methotrexate, cyclosporine, UV, oral retinoids, biologics



4. PUSTULAR PSORIASIS

Clinical Presentation

- sudden onset of erythematous macules and papules which evolve rapidly into pustules, very painful
- can be generalized or localized to palms/soles
- patient usually has history of psoriasis; may occur with sudden withdrawal from steroid therapy

Management

- methotrexate, oral retinoids, biologics

5. PSORIATIC ARTHRITIS

- 5 categories
 - asymmetric oligoarthritis
 - distal interphalangeal (DIP) joint involvement (predominant)
 - rheumatoid pattern (symmetric polyarthropathy)
 - psoriatic arthritis mutilans (most severe form)
 - predominant spondylitis or sacroiliitis
- see [Rheumatology, RH21](#)



Vesiculobullous Diseases



Bullous Pemphigoid

Clinical Presentation

- chronic autoimmune bullous eruption characterized by pruritic, tense, subepidermal bullae on an erythematous or normal skin base
- sites: flexor aspect of forearms, axillae, medial thighs, groin, abdomen, mouth (33%)

Pathophysiology

- IgG produced against dermal-epidermal basement membrane proteins (hemidesmosomes) leads to subepidermal bullae

Epidemiology

- 60-80 years old
- associated with malignancy (rarely)

Investigations

- immunofluorescence shows deposition of IgG and C3 in the basement membrane
- anti-basement membrane antibody (IgG) (pemphigoid antibody detectable in serum)

Prognosis

- generalized bullous eruption heals without scarring
- rarely fatal



Pemphigus Vulgaris vs. Bullous Pemphigoid

Vulgaris = Superficial, intraepidermal, flaccid lesions
Pemphigoid = Deeper, tense lesions at the dermal-epidermal junction

Management

- prednisone \pm steroid-sparing agents (e.g. azathioprine)
- topical potent steroids (clobetasol) may be as effective as systemic steroids
- tetracycline \pm nicotinamide is effective for some cases
- dapsone for milder cases

Dermatitis Herpetiformis**Clinical Presentation**

- grouped papules/vesicles/urticarial wheals on an erythematous base, associated with intense pruritus, burning, stinging
- almost always excoriated, rarely seen as blisters
- lesions grouped, bilaterally symmetrical
- sites: extensor surfaces of elbows/knees, sacrum, buttocks, scalp

Pathophysiology

- 90% have HLA B8, DR3, DQWZ
- 90% associated with gluten-sensitive enteropathy (celiac) (80% are asymptomatic)
- 30% have thyroid disease; some have intestinal lymphoma or iron/folate deficiency

Epidemiology

- 20-60 years old, M:F = 2:1

Management

- dapsone for pruritus
- gluten-free diet

Pemphigus Vulgaris**Clinical Presentation**

- autoimmune blistering disease characterized by flaccid, non-pruritic epidermal bullae/vesicles on an erythematous or normal skin base
- may present with erosions and secondary bacterial infection
- sites: mouth (90%), scalp, face, chest, axillae, groin, umbilicus
- Nikolsky's sign: sliding or rubbing pressure on skin \rightarrow separation of epidermis
- Asboe-Hansen sign: pressure applied to bulla causes it to extend laterally

Pathophysiology

- IgG produced against epidermal desmoglein 1 and 3 leads to intraepidermal bullae

Epidemiology

- 40-60 years old, higher prevalence in Jewish, Mediterranean, Asian populations
- paraneoplastic pemphigus may be associated with thymoma, myasthenia gravis, malignancy, and use of D-penicillamine

Investigations

- immunofluorescence: shows IgG and C3 deposition intraepidermally
- circulating serum anti-desmoglein IgG antibodies

Prognosis and Clinical Course

- begins with mouth lesions, followed by skin lesions
- first localized (6-12 months) then generalized
- lesions heal with hyperpigmentation but no scar
- may be fatal unless treated with immunosuppressive agents

Management

- prednisone 1.0-3.0 mg/kg until no new blisters, then 1.0-1.5 mg/kg until clear, then taper
- steroid-sparing agents: azathioprine, methotrexate, gold, cyclophosphamide, cyclosporine, intravenous immunoglobulin (IVIG), mycophenolate mofetil
- plasmapheresis for acutely high antibody levels

**Pemphigus Foliaceus**

An autoimmune intraepidermal blistering disease that is more superficial than pemphigus vulgaris due to antibodies against desmoglein 1, an intracellular adhesion molecule. Appears as crusted patches and erosions which can initially be managed with topical steroids if localized. Active widespread disease is treated like pemphigus vulgaris.

**Azathioprine**

Thiopurine methyltransferase (TPMT) levels should be measured before starting therapy. Individuals with low enzyme activity will experience greater immunosuppression.

Table 14. Summary of Vesiculobullous Diseases

	Bullous Pemphigoid	Dermatitis Herpetiformis	Pemphigus Vulgaris
Antibody	IgG	IgA	IgG
Site	Basement membrane	Dermal	Intraepidermal
Infiltrate	Eosinophils	Neutrophils	Eosinophils and neutrophils
Management	Systemic steroids Immunosuppressive agents Tetracycline Clobetasol cream	Gluten-free diet Dapsone	High dose steroids Immunosuppressive agent (e.g. Imuran®, mycophenolic acid)
Association	Malignancy (rarely)	Gluten enteropathy Thyroid disease Intestinal lymphoma	Malignancy with paraneoplastic pemphigus

Porphyria Cutanea Tarda

Clinical Presentation

- tense vesicles/bullae in photoexposed areas subjected to trauma
- facial hypertrichosis, brown hypermelanosis vesicles, and bullae in photodistribution (dorsum of hands and feet)
- sites: light-exposed areas subjected to trauma, dorsum of hands and feet, nose, and upper trunk

Pathophysiology

- autosomal dominant or sporadic skin disorder associated with the presence of excess heme
- associated with alcohol abuse, DM, drugs (estrogen therapy, NSAIDs), HIV, hepatitis C, increased iron indices

Epidemiology

- 30-40 years old, M>F

Investigations

- urine + 5% HCl shows orange-red fluorescence under Wood's lamp (UV rays)
- 24-hour urine for uroporphyrins (elevated)
- stool contains elevated coproporphyrins
- immunofluorescence shows IgE at dermal-epidermal junctions

Management

- discontinue aggravating substances (alcohol, estrogen therapy)
- phlebotomy to decrease body iron load
- low dose hydroxychloroquine

Drug Eruptions

Drug Hypersensitivity Syndrome

- fever followed by symmetrical bright red exanthematous eruption that may lead to internal organ involvement (hepatitis, arthralgia, nephritis, pneumonitis, lymphadenopathy, and/or hematologic abnormalities)
- classically occurs approximately 10 days after first exposure to the drug
- siblings at risk
- most common causes: sulfonamides and anticonvulsants (phenytoin, phenobarbital, carbamazepine, lamotrigine)
- 10% mortality if undiagnosed and untreated

Erythema Multiforme (EM), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)

- disorders with varying presence of characteristic skin lesions, blistering and mucous membrane involvement
- NOTE: EM is considered to be distinct from the SJS-TEN spectrum



Drug Hypersensitivity Syndrome Triad
Fever
Exanthematous Eruption
Internal Organ Involvement



Table 15. Comparison of Erythema Multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis

	Erythema Multiforme (EM)	Stevens-Johnson Syndrome (SJS)	Toxic Epidermal Necrolysis (TEN)
Lesion	Macules/papules with central vesicles Classic bull's-eye pattern of concentric light and dark rings (target lesions) Bilateral and symmetric All lesions appear within 72 hours No edema Lesion "fixed" for at least 7 days	EM with more mucous membrane involvement "Atypical lesions": red circular patch with dark purple centre "Sicker" (high fever) Sheet-like epidermal detachment in <10% (Nikolsky sign)	Severe mucous membrane involvement, and blistering "Atypical lesions": 50% have no target lesions Diffuse erythema then necrosis and sheet-like epidermal detachment in >30%
Sites	Dorsa of hands and forearms Mucous membrane involvement (lips, tongue, buccal mucosa) is possible Extremities with face > trunk Involvement of palms and soles	Generalized with prominent face and trunk involvement Palms and soles may be spared	Generalized Nails may also shed
Other Complications	Burning and stinging Recurrences Secondary bacterial infection	Scarring, contractures, eruptive nevocmelanocytic nevi, corneal scarring, blindness, phimosis and vaginal synechiae	Tubular necrosis and acute renal failure, epithelial erosions of trachea
Constitutional Symptoms	Weakness, malaise	Prodrome 1-14 days prior to eruption with fever and flu-like illness	High fever >38°C
Etiology	Infection: HSV, or <i>Mycoplasma pneumoniae</i>	15% are drug-related (NSAIDs, anticonvulsants, sulfonamides, penicillins) Occurs up to 1-3 weeks after drug exposure with more rapid onset upon rechallenge	50% are definitely drug related <5% are due to viral infection, immunization
Differential Diagnosis	Giant urticaria, granuloma annulare, mycosis fungoides, vasculitis	Scarlet fever, phototoxic, eruption, graft vs. host disease (GVHD), staphylococcal scalded skin syndrome (SSSS), exfoliative dermatitis, Kawasaki disease, paraneoplastic pemphigus	Scarlet fever, phototoxic eruption, GVHD, SSSS, exfoliative dermatitis
Course and Prognosis	Lesions last 2 weeks and heal without complications	4-6 week course 5% mortality	30% mortality due to fluid loss, regrowth of epidermis by 3 weeks, secondary infection
Management	Symptomatic treatment (oral antihistamines, oral antacids) Corticosteroids in severely ill (controversial) Prophylactic oral acyclovir for 6-12 months for herpes simplex virus (HSV)-associated EM with frequent recurrences	Prolonged hospitalization Withdraw suspect drug Intravenous fluids Corticosteroids (controversial) Infection prophylaxis Consider IVIG	As for Stevens-Johnson syndrome Admit to burn unit Debride frankly necrotic tissue Consider IVIG



Erythema multiforme is a clinical diagnosis. Reasonable evidence exists for the following as precipitating factors:

- HSV (predominant precipitating factor)
- *Mycoplasma pneumoniae*
- Orf virus

SCORTEN: A Severity-of-Illness Score for Toxic Epidermal Necrolysis

J Invest Dermatol 2000;115:149-153

Study: Develop and validate a specific severity-of-illness score for cases of TEN and compare to Simplified Acute Physiology Score and burn scoring system.

Patients: To develop score and evaluate other scores: 165 patients with SJS, SJS/TEN, or TEN admitted to the ICU. For validation, a separate database of 75 patients were used.

Outcome: Agreement between expected and actual mortality. Powers of discrimination.

Results: Seven different risk factors for death: age >40 y, malignancy, tachycardia above 120, initial epidermal detachment >10%, serum urea >10 mmol/L, serum glc >14 mmol/L, and bicarb <20 mmol/L. Expected score correlated with actual mortality (19.2% compared to 20%); whereas, the SAPS had poor agreement between expected and actual mortality (9.1% vs. 26.7%)

Exanthematous Eruptions (Maculopapular Eruptions/Morbilliform)

- symmetrical, widespread, erythematous patches or plaques ± scales
- the "classic" and most common adverse drug reaction
- often starts on trunk or areas of sun exposure
- may progress to generalized exfoliative dermatitis especially if the drug is continued
- most common causes: penicillin > sulfonamides > phenytoin
- see *Pediatric Exanthems*, D40

Fixed Drug Eruption

- sharply demarcated erythematous oval patches on the skin or mucous membranes
 - sites: face, mucosa, genitalia
 - reoccurs in same location upon subsequent exposure to the drug (fixed location)
- most common causes: antimicrobials (tetracycline, sulfonamides), anti-inflammatories, psychoactive agents (barbiturates), phenolphthalein

Photosensitivity Eruptions

- phototoxic reaction: “an exaggerated sunburn” confined to sun-exposed areas
- photoallergic reaction: an eczematous eruption that may spread to areas not exposed to light
- most common causes: chlorpromazine, doxycycline, thiazide diuretics, procainamide

Serum Sickness-Like Reaction

- a symmetric drug eruption resulting in fever, arthralgia, lymphadenopathy, and skin rash
- usually appears 5-10 days after drug
- skin manifestations: usually urticaria; can be morbilliform
- most common causes: cefaclor in kids; bupropion (Zyban®) in adults

Heritable Disorders

Ichthyosis Vulgaris

Clinical Presentation

- generalized hyperkeratosis leading to dry skin
- “fish-scale” appearance especially on extremities with sparing of flexural creases, palms and soles; scaling without inflammation

Pathophysiology

- abnormal retention of hyperkeratosis
- scaling without inflammation

Epidemiology

- 1:300 incidence
- autosomal dominant inheritance
- associated with atopic dermatitis and keratosis pilaris

Management

- immersion in bath and oils
- emollient or humectant creams, and creams or oils containing urea

Neurofibromatosis (Type I; von Recklinghausen’s Disease)

Clinical Presentation

- diagnostic criteria includes 2 or more of the following:
 1. more than 6 café-au-lait spots >1.5 cm in an adult, and more than 5 café-au-lait spots >0.5 cm in a child under age 5
 2. axillary or inguinal freckling
 3. iris hamartomas (Lisch nodules)
 4. optic gliomas
 5. neurofibromas
 6. distinctive bony lesion
 7. first degree relative with neurofibromatosis type 1
- associated with pheochromocytoma, astrocytoma, bilateral acoustic neuromas, bone cysts, scoliosis, precocious puberty, developmental delay, and renal artery stenosis

Pathophysiology

- autosomal dominant disorder with excessive and abnormal proliferation of neural crest elements (Schwann cells, melanocytes)
- linked to absence of neurofibromin (a tumour suppressor gene)

Epidemiology

- incidence 1:3,000

Management

- follow closely for malignancy, transformation of neurofibroma to neurofibrosarcoma
- excise suspicious or painful lesions
- see [Pediatrics](#), P86

Vitiligo



Clinical Presentation

- primary pigmentary disorder characterized by hypopigmentation and depigmentation
- acquired destruction of melanocytes characterized by sharply margined white patches
- associated with streaks of depigmented hair, chorioretinitis
- sites: extensor surfaces and periorificial areas (mouth, eyes, anus, genitalia)
- Koebner phenomenon "isomorphic response": may be precipitated by trauma

Pathophysiology

- acquired autoimmune destruction of melanocytes

Epidemiology

- 1% incidence, polygenic
- 30% with positive family history

Investigations

- rule out associated autoimmune diseases: thyroid disease, pernicious anemia, Addison's disease, Type I DM
- Wood's lamp to detect lesions: illuminates UV light onto skin to detect patches of amelanosis

Management

- sun avoidance and protection
- topical immunomodulator (i.e. tacrolimus, pimecrolimus) or a topical steroid for 6-12 months prior to attempting phototherapy
- PUVA
- camouflage preparations
- "bleaching" normal pigmented areas (i.e. hydroquinone 20%) if widespread loss of pigmentation

Interventions for Vitiligo

Cochrane Database of Syst Rev 2010; Issue 1

Study: Systematic review of randomized controlled trials.

Patients: 3139 participants with vitiligo.

Intervention: Topical treatments, light therapies, oral treatments, surgical methods, and psychological therapies

Outcome: >75% repigmentation, adverse effects

Results: Moderate evidence exists for the use of topical corticosteroids to induce repigmentation. However, adverse effects are observed with long-term use. Topical use of non-steroidal immunomodulators (i.e. tacrolimus), especially in combination with light therapies, has also been shown to induce repigmentation. However, long-term use may theoretically increase the risk for skin cancer. In general, combination therapy including some form of light therapy had the most significant improvement. Sustained repigmentation (>2 years) has not been reported and thus results should be treated with caution.

Randomized Double-blind Trial of Treatment of Vitiligo

Arch Dermatol 2007; 143: 578

Study: Double-blinded randomized study.

Patients: 56 patients with nonsegmental vitiligo.

Interventions: PUVA or NB-UVB twice per week

Outcome: % of body surface area that was repigmented and colour match compared to unaffected skin at 48 sessions of therapy, at the end of therapy, and at 12 months.

Results: NB-UVB is superior to PUVA. 64% of 25 patients in the NB-UVB group showed greater than 50% improvement in BSA compared to 36% of 25 patients in the PUVA group. Colour match was greater in the NB-UVB group than the PUVA group ($P < 0.001$). After 48 sessions BSA change was greater in the NB-UVB group ($P = .007$) this benefit was maintained at 12 months.

Infections

Bacterial Infections

- often involve the epidermis, dermis, hair follicles or periungual region ± systemic

SUPERFICIAL SKIN (EPIDERMAL)

Table 16. Comparison of Impetigo Vulgaris and Bullous Impetigo

	Impetigo Vulgaris	Bullous Impetigo
Clinical Presentation	Acute purulent infection which appears vesicular; progresses to golden yellow "honey-crusted" lesions surrounded by erythema Sites: commonly face, arms, legs and buttocks	Scattered, thin-walled bullae containing clear yellow or slightly turbid fluid with no surrounding erythema Sites: trunk, intertriginous areas, face
Etiology	Group A beta-hemolytic <i>Streptococcus</i> (GAS), <i>S. aureus</i> , or both	<i>S. aureus</i> group II elaborating exfoliating toxin
Epidemiology	Preschool and young adults living in crowded conditions, poor hygiene, neglected minor trauma	Neonates and older children, can be epidemic
Differential Diagnosis	Infected eczema, HSV, varicella virus	Bullous drug eruption, pemphigus vulgaris, bullous insect bites, thermal burns
Investigations	Gram stain and culture of lesion fluid or biopsy	Same as impetigo vulgaris
Management	Remove crusts, use saline compresses and topical antiseptic soaks bid Topical antibacterials such as 2% mupirocin or fusidic acid TID; continue for 7-10 days after resolution Systemic antibiotics such as cloxacillin or cephalixin for 7-10 days	Cloxacillin for 7-10 days Topical antibacterials such as fusidic acid or mupirocin; continue for 7-10 days after oral antibiotic is stopped Complication: high levels of toxin in immunocompromised or young children may lead to generalized skin peeling or staphylococcal scalded skin syndrome (SSSS)





DEEPER SKIN (DERMAL)

Table 17. Comparison of Erysipelas and Cellulitis

	Erysipelas	Cellulitis
Clinical Presentation	Involves upper dermis Confluent, erythematous, raised, warm plaque, well demarcated Very painful (once called St. Anthony's fire) Sites: face and legs Systemic symptoms: fever, chills, headache, weakness (if present, sign of more serious infection)	Involves lower dermis/subcutaneous fat Unilateral erythematous flat lesion, often with vesicles poorly demarcated, not uniformly raised Tender Sites: commonly on legs Systemic symptoms (uncommon): fever, leukocytosis, lymphadenopathy
Etiology	GAS	GAS, <i>S. aureus</i> (large sized wounds), <i>H. influenzae</i> (periocular), <i>Pasteurella multocida</i> (dog/cat bite)
Complications	Scarlet fever, streptococcal gangrene, fat necrosis, coagulopathy Spreads via lymphatics	Uncommon
Differential Diagnosis	DVT (less red, less hot, smoother), superficial phlebitis, contact dermatitis, photosensitivity reaction, stasis dermatitis, panniculitis, vasculitis	Same as erysipelas
Investigations	Clinical diagnosis: rarely do skin/blood culture If suspect necrotizing fasciitis: do immediate biopsy and frozen section, histopathology	Same as erysipelas
Management	1st line: penicillin, cloxacillin or cefazolin 2nd line: clindamycin or cephalexin If allergic to penicillin use erythromycin	1st line: cloxacillin or cefazolin/cephalexin 2nd line: erythromycin or clindamycin Children: cefuroxime If diabetes mellitus (foot infections): trimethoprim-sulfamethoxazole (TMP/SMX) and metronidazole

COMMON HAIR FOLLICLE INFECTIONS

Table 18. Comparison of Superficial Folliculitis, Furuncles and Carbuncles

	Superficial Folliculitis	Furuncles (Boils)	Carbuncles
Clinical Presentation	Superficial infection of the hair follicle (versus pseudofolliculitis: inflammation of follicle due to friction, irritation, or occlusion) Acute lesion consists of a dome-shaped pustule at the mouth of hair follicle Pustule ruptures to form a small crust Sites: primarily scalp, shoulders, anterior chest, upper back, other hairbearing areas	Red, hot, tender, inflammatory nodules with central yellowish point, which forms over summit and ruptures Involves subcutaneous tissue that arises from a hair follicle Sites: hair-bearing skin (thigh, neck, face, axillae, perineum, buttocks)	Deep-seated abscess formed by multiple coalescing furuncles Usually in areas of thicker skin Occasionally ulcerates Lesions drain through multiple openings to the surface Systemic symptoms may be associated
Etiology	Normal non-pathogenic bacteria (<i>Staphylococcus</i> – most common; <i>Pseudomonas</i> – hot tub) <i>Pityrosporum</i>	<i>S. aureus</i>	<i>S. aureus</i>
Management	Antiseptic (Hibitane®) Topical antibacterial (fusidic acid, mupirocin, or erythromycin) Oral cloxacillin for 7-10 days	Incise and drain large carbuncles to relieve pressure and pain If afebrile: hot wet packs, topical antibiotic If febrile/cellulitis: culture blood and aspirate pustules (Gram stain and C&S) Cloxacillin for 1-2 weeks (especially for lesions near external auditory canal/nose, with surrounding cellulitis, and not responsive to topical therapy)	Same as for furuncles



Dermatophytoses

Clinical Presentation

- infection of skin, hair and nails caused by dermatophytes (fungi that live within the epidermal keratin and do not penetrate deeper structures)

Pathophysiology

- digestion of keratin by dermatophytes results in scaly skin, broken hairs, crumbling nails

Etiology

- Trichophyton*, *Microsporum*, *Epidermophyton* species (*Pityrosporum* is a superficial yeast)

Investigations

- skin scrapings, hair, and/or nail clippings analyzed with potassium hydroxide (KOH) prep to look for hyphae and mycelia

Management

- topicals as first line agents for tinea corporis/cruris and tinea pedis (interdigital type):
 - e.g. clotrimazole or terbinafine cream applied OD or BID, until one week after complete resolution of lesions
- oral therapy is indicated for onychomycosis or tinea capitis:
 - e.g. terbinafine (Lamisil® – liver toxicity, CYP 2D6 inhibitor) or itraconazole (Sporanox® – heart failure reported, CYP 3A4 inhibitor)

Table 19. Different Manifestations of Dermatophyte Infection

	Clinical Presentation	Differential Diagnosis	Investigations	Management
Tinea Capitis	Round, scaly patches of alopecia, possibly with broken off hairs; pruritic Sites: scalp, eyelashes, and eyebrows; involving hair shafts and follicles Kerion (boggy, elevated, purulent inflamed nodule/plaque) may form secondary to infection by bacteria and result in scarring May have occipital lymphadenopathy Affects children (mainly black), immunocompromised adults Very contagious and may be transmitted from barber, hats, theatre seats, pets	Alopecia areata, psoriasis, seborrheic dermatitis, trichotillomania	Wood's light examination of hair: green fluorescence only for <i>Microsporum</i> infection Culture of scales/hair shaft Microscopic examination of KOH preparation of scales or hair shafts	Griseofulvin x 8 weeks or terbinafine (Lamisil®) x 2-4 weeks NB: oral agents are required to penetrate the hair root Adjunctive antifungal shampoos or lotions may be helpful (e.g. selenium sulfide, ketoconazole, ciclopirox)
Tinea Corporis (Ringworm)	Pruritic, scaly, round/oval plaque with active erythematous margin and central clearing Site: trunk, limbs, face	Granuloma annulare, pityriasis rosea, psoriasis, seborrheic dermatitis	Microscopic examinations of KOH prep of scales shows hyphae Culture of scales	Topicals: 1% clotrimazole or 2% miconazole BID for 2-4 weeks
Tinea Cruris ("Jock Itch")	Scaly patch/plaque with a well-defined, curved border and central clearing Pruritic, erythematous, dry/macerated Site: medial thigh	Candidiasis (involvement of scrotum and satellite lesions), contact dermatitis, erythrasma	Same as for tinea corporis	Topicals: 1% clotrimazole or 2% miconazole BID for 2-4 weeks
Tinea Pedis (Athlete's Foot)	Pruritic scaling and/or maceration of the web spaces and powdery scaling of soles Acute infection: interdigital (esp. 4th web space) red/white scales, vesicles, bullae, often with maceration Secondary bacterial infection is common Chronic: non-pruritic, pink, scaling keratosis on soles and sides of feet May present as flare-up of chronic tinea pedis Predisposing factors: heat, humidity, occlusive footwear	Atopic dermatitis, contact dermatitis, dyshidrotic dermatitis, erythrasma, intertrigo (interdigital), psoriasis	Same as for tinea corporis	Topicals: 1% clotrimazole or 2% miconazole BID for 2-4 weeks
Tinea Manuum	Primary fungal infection of the hand is rare; usually associated with tinea pedis Acute: blisters at edge of red areas on hands Chronic: single dry scaly patch	Atopic dermatitis, contact dermatitis, granuloma annulare, psoriasis	Same as for tinea corporis	Topicals: 1% clotrimazole or 2% miconazole BID for 2-4 weeks
Tinea Unguium (Onychomycosis)	Crumbling, distally dystrophic nails; yellowish, opaque with subungual hyperkeratotic debris Toenail infections usually precede fingernail infections <i>T. rubrum</i> (90% of all toenail infections)	Psoriasis, lichen planus, contact dermatitis, traumatic onychodystrophies, bacterial infections	Microscopic examinations of KOH prep of scales from subungual scraping shows hyphae Culture of subungual scraping or nail clippings on Sabouraud's agar	Terbinafine (Lamisil®) (6 weeks for fingernails, 12 weeks for toenails) Itraconazole (Sporanox®) 7 days on, 3 weeks off (2 pulses for fingernails, 3 pulses for toenails) Topical: ciclopirox (Penlac®); nail laquer

Parasitic Infections



SCABIES

Clinical Presentation

- a transmissible parasitic skin infection due to *Sarcoptes scabiei*, a mite, characterized by superficial burrows, intense pruritus (especially nocturnal), and secondary infection
- primary lesion: superficial linear burrows
- secondary lesion: small urticarial crusted papules, eczematous plaques, excoriations
- sites: axillae, groin, buttocks, hands/feet (especially web spaces), sparing of head and neck (except in infants)

Pathogenesis

- scabies mite remains alive 2-3 days on clothing/sheets
- incubation of 1 month, then pruritus begins
- re-infection followed by hypersensitivity in 24 hours

Etiology

- *Sarcoptes scabiei*, a mite
- risk factors: sexual promiscuity, crowding, poverty, nosocomial, immunocompromised

Differential Diagnosis

- asteatotic eczema, dermatitis herpetiformis (vesicles, urticaria, eosinophilia, no burrows), lichen simplex chronicus (neurodermatitis)

Investigations

- microscopic examination of root and content of burrow with KOH for mite, eggs, feces

Management

- bathe, then apply permethrin 5% cream (i.e. Nix®) from neck down to soles of feet (must be left on for 8-14 hours and requires second treatment 7 days after first treatment)
- change underwear and linens; wash with detergent in hot water cycle then machine dry
- ± antihistamine
- treat family and contacts
- pruritus may persist for 2-3 weeks due to prolonged hypersensitivity reaction

LICE (PEDICULOSIS)**Clinical Presentation**

- intensely pruritic red excoriations, morbilliform rash, caused by louse (a parasite)
- scalp lice: nits (i.e. louse eggs) on hairs
 - red excoriated skin with secondary bacterial infection, lymphadenopathy
- pubic lice: nits on hairs
 - excoriations
- body lice: nits and lice in seams of clothing
 - excoriations and secondary infection mainly on shoulders, belt-line and buttocks

Differential Diagnosis

- bacterial infection of scalp, seborrheic dermatitis

Management

- permethrin 1% (Nix® cream rinse) (ovicidal) or permethrin 1% (RC & Cor®, Kwellada-P® shampoo)
- comb hair with fine-toothed comb using dilute vinegar solution to remove nits
- repeat in 7 days after first treatment
- change clothing and linens; wash with detergent in hot water cycle then machine dry



Viral Infections

HERPES SIMPLEX**Clinical Presentation**

- herpetiform (i.e. grouped) vesicles on an erythematous base on skin or mucous membranes
- transmitted via contact with erupted vesicles or via asymptomatic viral shedding
- **primary**
 - children and young adults
 - usually asymptomatic; may have high fever, regional lymphadenopathy, malaise
 - followed by antibody formation and latency of virus in nerve root ganglion
- **secondary**
 - recurrent form seen in adults; much more common than primary
 - prodrome: tingling, pruritus, pain
 - triggers for recurrence: fever, sunburn, physical trauma, menstruation, emotional stress, upper respiratory tract infection (URTI)
- potential complications
 - dendritic corneal ulcer
 - erythema multiforme (EM)
 - herpes simplex encephalitis
 - HSV infection on atopic dermatitis causing Kaposi's varicelliform eruption (eczema herpeticum)
- 2 biologically and immunologically different subtypes: **HSV-1** and **HSV-2**

HSV-1

- typically “cold sores” (grouped vesicles at the mucocutaneous junction which quickly burst)
- recurrent on face, lips but NOT on mucous membranes (unlike aphthous ulcers)

Management

- treat during prodrome to prevent vesicle formation
- topical antiviral (Zovirax®) cream, apply 5-6x/day, 4-7 days for facial/genital lesions
- oral antivirals are far more effective and have an easier dosing schedule

HSV-2

- sexually transmitted; incubation 2-20 days
- gingivostomatitis: entire buccal mucosa involved with erythema and edema of gingiva
- vulvovaginitis: edematous, erythematous, extremely tender, profuse vaginal discharge
- urethritis: watery discharge in males
- recurrent on vulva, vagina, penis for 5-7 days
- diagnosis
 - negative darkfield, negative serology for syphilis, negative bacterial cultures
 - Tzanck smear with Giemsa stain shows multinucleated giant epithelial cells
 - tissue culture and electron microscopy of vesicular fluid
 - skin biopsy
 - antibody titres increase one week after primary infection only (no increase with recurrent lesions)
- DDx of genital ulcers: *Candida balanitis*, chancroid, multiple syphilitic chancres

Management

- rupture vesicle with sterile needle
- wet dressing with aluminum subacetate solution, Burow's compression, or betadine solution
- 1st episode: acyclovir 200 mg PO 5 times a day x 10 days
 - maintenance: acyclovir 400 mg PO BID
- famciclovir and valacyclovir may be substituted and have better enteric absorption
- in case of herpes genitalis, look for and treat any other sexually-transmitted infections



Both HSV-1 and HSV-2 can occur on face or genitalia.

HERPES ZOSTER (SHINGLES)**Clinical Presentation**

- unilateral dermatomal eruption occurring 3-5 days after pain and paresthesia of that dermatome
- vesicles, bullae, and pustules on an erythematous, edematous base
- lesions may become eroded/ulcerated and last days – weeks
- pain is pre-herpetic, synchronous with rash, or post-herpetic
- severe post-herpetic neuralgia often occurs in elderly
- Hutchinson's sign: involvement of tip of nose suggests eye involvement
- distribution: thoracic (50%), trigeminal (10-20%), cervical (10-20%); disseminated in HIV



Herpes Zoster typically involves a single dermatome; lesions rarely cross the midline.

Etiology

- caused by varicella zoster in a person who has already had the primary infection (chicken pox)
- risk factors: immunosuppression, old age, occasionally associated with hematologic malignancy

Differential Diagnosis

- before thoracic skin lesions occur, must consider other causes of chest pain
- contact dermatitis, localized bacterial infection, zosteriform herpes simplex virus (more pathogenic for the eyes than varicella zoster)

Management

- compress with normal saline, burrow's, or betadine solution
- analgesics (NSAIDs, amitriptyline)
- for patients over 50 years old, with severe acute pain or ophthalmic involvement: famciclovir or valacyclovir for 7 days or acyclovir for 7 days if immunocompromised; must initiate within 72 hours to be of benefit
- gabapentin 300-600 mg PO TID for post-herpetic neuralgia

MOLLUSCUM CONTAGIOSUM

Clinical Presentation

- discrete dome-shaped and umbilicated pearly, white papules caused by DNA pox virus (*Molluscum contagiosum* virus (MCV))
- sites: eyelids, beard (likely spread by shaving), neck, axillae, trunk, perineum, buttocks

Etiology

- *Molluscum contagiosum* is spread via direct contact, auto-inoculation, sexual contact
- common in children and AIDS patients

Management

- topical cantharidin (a keratolytic)
- liquid nitrogen cryotherapy
- curettage
- Aldara® (imiquimod): immune modulator that produces a cytokine inflammation

WARTS (VERRUCA VULGARIS) (HUMAN PAPILLOMA VIRUS (HPV) INFECTIONS)

Table 20. Different Manifestations of HPV Infection

	Definition and Clinical Features	Differential Diagnosis
Verruca Vulgaris (Common Warts)	Hyperkeratotic, elevated discrete epithelial growths with papillated surface caused by HPV – at least 80 types are known Located at trauma sites: fingers, hands, knees of children and teens Paring of surface reveals punctate, red-brown specks (dilated capillaries)	Molluscum contagiosum, seborrheic keratosis
Verruca Plantaris (Plantar Warts) and Verruca Palmaris (Palmar Warts)	Hyperkeratotic, shiny, sharply marginated growths Commonly HPV 1, 2, 4, 10 Located at pressure sites: heads of metatarsal, heels, toes Paring of surface reveals red-brown specks (capillaries), interruption of epidermal ridges	Need to scrape (“pare”) lesions to differentiate wart from callus and corn (see side bar D8)
Verruca Planae (Flat Warts)	Multiple discrete, skin coloured, flat topped papules grouped or in linear configuration Common in children Commonly HPV 3, 10 Sites: face, dorsa of hands, shins, knees	Syringoma, seborrheic keratosis, molluscum contagiosum, lichen planus
Condyloma Acuminata (Genital Warts)	Skin-coloured pinhead papules to soft cauliflower like masses in clusters Commonly HPV 6 and 11 HPV 16, 18, 31, 33 cause cervical dysplasia, squamous cell cancer and invasive cancer Sites: genitalia and perianal areas Often occurs in young adults, infants, children Can be asymptomatic, lasting months to years Highly contagious, transmitted sexually and non-sexually (e.g. Koebner phenomenon via scratching, shaving), and can spread without clinically apparent lesions Investigations: acetowhitening (subclinical lesions seen with 5% acetic acid x 5 minutes and hand lens) Complications: fairy-ring warts (satellite warts at periphery of treated area of original warts)	Condyloma lata (secondary syphilitic lesion, darkfield strongly +ve), Molluscum contagiosum

Table 21. Management of Warts

Management	Type of Wart	Notes
Destructive		
Liquid nitrogen/electrodesiccation	All	Dyschromia, pain, 10-30 seconds
Surgery	Resistant	Scar, recurrence
Laser	Resistant	CO ₂ and Nd: Yag lasers
Caustic Acids		
Cantharidin (topical)	Small, common	Keratolytic irritation, blisters, hyperpigmentation
Mono-, di-, or tri-chloroacetic acid	Common	Irritation, blisters, scar
Chemotherapeutic Agents		
Podophyllotoxin*	Genital	Erythema, erosions, ulcers, pain
Bleomycin (intralesional)*	Common	Pain, nail loss/dystrophy, Raynaud's phenomenon
Hypersensitivity Agents		
Dinitrochlorobenzene (DNCB)	Common, plantar	Causes an allergic/hypersensitivity reaction
Immune Response Modifiers	Genital	Erythema, burning, erosion
5% imiquimod cream (Aldara®)*	All	
Miscellaneous		
No treatment	Common	65-90% resolve spontaneously over several years
Salicylic acid 40% minimum	Common, plantar	Over the counter (OTC), use with occlusion
Tretinoin (topical)*	Flat	Irritation
Cimetidine (oral)*	Resistant	Best in children
Canthone plus	Common, plantar	Cantharidin + podophyllin + salicylic acid
Duct tape		
± occlusion/callous scraping/paring		

*Avoid in pregnancy

Yeast Infections

CANDIDIASIS

Candidal Paronychia

- painful red swellings of periungual skin
- management: topical agents not as effective; oral antifungals recommended

Candidal Intertrigo

- macerated/eroded erythematous patches that may be covered with papules and pustules, located in intertriginous areas often under breast, groin, or interdigitally
- peripheral "satellite" pustules
- predisposing factors: obesity, diabetes, systemic antibiotics, immunosuppression, malignancy
- starts as non-infectious maceration from heat, moisture and friction
- management: keep area dry, miconazole, ketoconazole/clotrimazole cream bid until rash clears

PITYRIASIS (TINEA) VERSICOLOUR

Clinical Presentation

- chronic asymptomatic superficial fungal infection with brown/white scaling macules
- affected skin darker than surrounding skin in winter, lighter in summer (does not tan)
- sites: upper trunk most common

Pathophysiology

- microbe produces carboxylic acid → inflammatory reaction inhibiting melanin synthesis yielding variable pigmentation
- affinity for sebaceous glands; require fatty acids to survive

Etiology

- *Pityrosporum ovale* (*Malassezia furfur*)
- also associated with folliculitis and seborrheic dermatitis
- predisposing factors: summer, tropical climates, Cushing's syndrome, prolonged corticosteroid use

Investigations

- microscopic examination KOH prep of scales for hyphae and spores

Management

- scrub off scales with soap and water
- selenium sulfide body lotion
- ketoconazole cream or PO daily for 10 days if more extensive



Treatment for Skin Warts

First Line Therapies

Salicylic acid preparations (patches, solutions, creams, ointments)
Silver nitrate stick
Topical cantharone
Glutaraldehyde
Occlusive methods (duct tape)

Second Line Therapies

Liquid nitrogen cryotherapy
Topical imiquimod

Third Line Therapies

Curettage
Cautery
Surgery
Laser
Oral cimetidine (particularly children)
Topical 5-fluorouracil
Topical tretinoin (flat warts)
Localized heat therapy
Intralesional bleomycin (plantar warts)



Treatment for Anogenital Warts

First line therapies

Imiquimod 5% cream
Podophyllotoxin (solution, cream, or gel)
Podophyllin resin
Cryotherapy

Second line therapies

Trichloroacetic acid
Topical 5-fluorouracil
Electrodesiccation
Surgical excision (with cold steel or scissors)
CO₂ laser



Oral Terbinafine (Lamisil®) is not effective because it is not secreted by sebaceous glands.



Sexually Transmitted Infections

SYPHILIS

Clinical Presentation

- characterized initially by a painless ulcer (chancre)
- following inoculation, systemic infection with secondary and tertiary stages

Etiology

- *Treponema pallidum*
- transmitted sexually, congenitally, or rarely by transfusion

Table 22. Stages of Syphilis

	Primary Syphilis	Secondary Syphilis	Tertiary Syphilis
Clinical Presentation	<ul style="list-style-type: none"> • Single red, indurated, painless chancre, that develops into painless ulcer with raised border and scanty serous exudate • Chancre develops at site of inoculation after 3 weeks of incubation and heals in 4-6 weeks; chancre may also develop on lips or anus • Regional non-tender lymphadenopathy appears <1 week after onset of chancre • DDx: chancroid (painful), HSV (multiple lesions) 	<ul style="list-style-type: none"> • Presents 2-6 months after primary infection (patient may not recall presence of primary chancre) • Associated with generalized lymphadenopathy, splenomegaly, headache, chills, fever, arthralgias, myalgias, malaise, photophobia • Lesions heal in 1-5 weeks and may recur for 1 year • 3 types of lesions: <ol style="list-style-type: none"> 1. Macules and papules: flat top, scaling, non-pruritic, sharply defined, circular/annular rash (DDx: pityriasis rosea, tinea corporis, drug eruptions, lichen planus) 2. Condyloma lata: wart-like moist papules around genital/perianal region 3. Mucous patches: macerated patches mainly found in oral mucosa 	<ul style="list-style-type: none"> • Extremely rare • 3-7 years after secondary • Main skin lesion: 'Gumma' – a granulomatous non-tender nodule
Investigations	<ul style="list-style-type: none"> • CANNOT be based on clinical presentation alone • VDRL negative – repeat weekly for 1 month • Fluorescent treponemal antibody-syphilis (FTA-ABS) test has greater sensitivity and may detect disease earlier in course • Darkfield examination – spirochete in chancre fluid or lymph node aspirate 	<ul style="list-style-type: none"> • VDRL positive • FTA-ABS +ve; –ve after 1 year following appearance of chancre • Darkfield +ve in all secondary 	<ul style="list-style-type: none"> • As in primary syphilis, VDRL can be falsely negative
Management	<ul style="list-style-type: none"> • Penicillin G, 2.4 million units IM, single dose 	<ul style="list-style-type: none"> • As for primary syphilis 	<ul style="list-style-type: none"> • Treatment: penicillin G, 2.4 million units IM weekly

GONOCOCCEMIA

Clinical Presentation

- disseminated gonococcal infection
- hemorrhagic, tender, pustules on a purpuric/petechial background
- sites: distal aspects of extremities
- associated with fever, arthritis, urethritis, proctitis, pharyngitis and tenosynovitis
- neonatal conjunctivitis if infected via birth canal

Etiology

- *Neisseria gonorrhoeae*

Management

- notify Public Health authorities
- screen for other sexually transmitted infections (STIs)
- cefixime 400 mg PO (drug of choice) or ceftriaxone 125 mg IM



Natural History of Untreated Syphilis

- Inoculation
- Primary syphilis (10-90 d after infection)
- Secondary syphilis (simultaneous to primary syphilis or up to 6 mo after healing of primary lesion)
- Latent syphilis
- Tertiary syphilis (2-20 y)



Latent Syphilis

The period between healing of clinical lesions and appearance of late manifestations. 70% of untreated patients will remain in this stage for the rest of their lives and are immune to new primary infection.

Pre-Malignant Skin Conditions

- **actinic keratosis:** 1-10% become squamous cell carcinoma (SCC)
- **dysplastic nevi:** risk of malignant melanoma (see Table 5)

Leukoplakia

Clinical Presentation

- a morphologic term describing homogenous or speckled white plaques with sharply demarcated borders
- sites: oropharynx, most often floor of the mouth, soft palate, and ventral/lateral surfaces of the tongue

Pathophysiology

- precancerous or premalignant condition
- oral form is strongly associated with tobacco use and alcohol consumption

Epidemiology

- 1-5% prevalence in adult population after 30 years of age; peak at age 50
- M>F, fair-skinned
- most common oral mucosal premalignant lesion

Differential Diagnosis

- lichen planus, oral hairy leukoplakia

Investigations

- biopsy is mandatory because it is premalignant

Management

- low risk sites on buccal/labial mucosal or hard palate: eliminate carcinogenic habits, follow-up
- moderate/dysplastic lesions: excision, cryotherapy

Malignant Skin Tumours



Basal Cell Carcinoma (BCC)



Subtypes

- noduloulcerative (typical)
 - skin-coloured papule/nodule with rolled, translucent ("pearly") telangiectatic border and depressed/eroded/ulcerated centre
- pigmented variant
 - flecks of pigment in translucent lesion with surface telangiectasia
 - may mimic malignant melanoma
- superficial variant
 - flat, tan to red-brown plaque, often with scaly, pearly border and fine telangiectasia at margin
- sclerosing variant
 - flesh/yellowish-coloured, shiny papule/plaque with indistinct borders

Pathophysiology

- malignant proliferation of basal cells of the epidermis
 - low grade cutaneous malignancy, locally aggressive (primarily tangential growth), rarely metastatic
 - usually due to UVB light, therefore >80% on face
 - may also be caused by scar formation, radiation, trauma, arsenic exposure, or genetic predisposition (Gorlin syndrome)

Epidemiology

- most common malignancy in humans
- 75% of all malignant skin tumours >40 years, increased prevalence in the elderly
- M>F, skin phototypes I and II, chronic cumulative sun exposure

Differential Diagnosis

- benign: sebaceous hyperplasia, intradermal melanocytic nevus, dermatofibroma
- malignant: nodular malignant melanoma, SCC



Work-up of Nonmelanoma Skin Cancers (NMSC)

- **History:** duration, growth rate, family/personal hx of skin cancer, prior therapy to the particular lesion.
- **Physical:** location, size, whether circumscribed, tethering to deep structures, full skin exam, lymph node exam
- **Biopsy:** if shallow lesion do shave biopsy; otherwise punch biopsy.



Margins

- **Smaller lesions:** electrodesiccation and curettage with 2-3 mm margin of normal skin.
- **Deep infiltrative lesions:** surgical excision with 3-5 mm margins beyond visible and palpable tumour border; may require skin graft or flap.

Management

- imiquimod 5% cream (Aldara®) or cryotherapy is indicated for superficial BCCs on the trunk
- shave excision + electrodesiccation and curettage for all other types of BCCs
- microscopically controlled, minimally invasive, stepwise excision (Mohs surgery) or radiotherapy for lesions on the face or in areas that are difficult to reconstruct
- life-long follow-up
- 95% cure rate if lesion <2 cm in diameter

Cutaneous T-Cell Lymphoma

Clinical Presentation

- **Mycosis fungoides** (limited superficial type)
 - characterized by: erythematous patches/plaques/nodules/tumours, which may be pruritic and poikilodermic (atrophy, telangiectasia, hyperpigmentation)
 - common sites include: trunk, buttocks, proximal limbs
 - mildly symptomatic, usually excellent prognosis for early disease
- **Sezary syndrome** (widespread systemic type)
 - rare variant characterized by: universal erythroderma ("redman syndrome"), lymphadenopathy, WBC >20 x 10⁹/L with Sezary cells
 - associated with intense pruritus, alopecia, palmoplantar hyperkeratosis, and systemic symptoms (fatigue, fever)
 - often fatal

Pathophysiology

- clonal proliferation of skin-homing CD4 T cells

Epidemiology

- >50 years old, M:F 2:1

Differential Diagnosis

- tinea corporis, nummular dermatitis, psoriasis, discoid lupus erythematosus, Bowen's disease

Investigations

- skin biopsy (histology, "lymphocyte antigen cell" markers, TcR gene arrangement)
- blood smear looking for Sezary cells or flow cytometry (e.g. CD4:CD8 >10 is Sezary)
- imaging (for systemic involvement)

Management

- **Mycosis fungoides**
 - treatment is dependent on stage of disease
 - topical steroids and/or PUVA, narrow band (311-313 nm), UVB (NB-UVB)
- **Sezary syndrome**
 - oral retinoids and interferon
 - extra-corporeal photophoresis
 - may need radiotherapy for total skin electron beam radiation
 - may maintain on UV therapy



Malignant Melanoma (MM)

Clinical Presentation

- malignant characteristics of a mole: see mnemonic "ABCDE"
- sites: skin, mucous membranes, eyes, CNS

Subtypes of Malignant Melanoma

- **lentigo maligna**
 - malignant melanoma *in situ* (normal and malignant melanocytes confined to the epidermis)
 - 2-6 cm, tan/brown/black uniformly flat macule or patch with irregular borders
 - lesion grows radially and produces complex colours
 - sites: face, sun exposed areas
 - 1/3 evolve into lentigo maligna melanoma
- **lentigo maligna melanoma** (15% of all melanomas)
 - malignant melanocytes invading into the dermis
 - associated with pre-existing solar lentigo, not pre-existing nevi
 - flat, brown, stain-like, gradually enlarging with loss of skin surface markings
 - with time, colour changes from uniform brown to dark brown with black and blue
 - found on all skin surfaces, especially those often exposed to sun

**Does this Patient have a Mole or Melanoma?**

JAMA 1998; 279(9): 696-701

ABCDE checklist

Asymmetry
Border (irregular)
Colour (varied)
Diameter (increasing or >6 mm)
Enlargement, elevation, evolution

Sensitivity 92% (CI 82-96%)
Specificity 100% (CI 54-100%)

- **superficial spreading melanoma** (60-70% of all melanomas)
 - atypical melanocytes initially spread laterally in epidermis then invade the dermis
 - irregular, indurated, enlarging plaques with red/white/blue discolouration, focal papules or nodules
 - ulcerate and bleed with growth
- **nodular melanoma** (30% of all melanomas)
 - atypical melanocytes that initially grow vertically with little lateral spread
 - uniformly ulcerated, blue-black, and sharply delineated plaque or nodule
 - rapidly fatal
- **acrolentiginous melanoma** (5% of all melanomas)
 - ill-defined dark brown, blue-black macule
 - palmar, plantar, subungual skin
 - melanomas on mucous membranes have poor prognosis

Pathophysiology

- malignant neoplasm of pigment forming cells (melanocytes and nevus cells)

Epidemiology

- incidence 1:100
- risk factors: numerous moles, fair skin, red hair, positive personal/family history, large congenital nevi, familial dysplastic nevus syndrome
- most common sites: back (males), calves (females)
- worse prognosis if: male, on scalp, hands, feet, late lesion, no pre-existing nevus present

Differential Diagnosis

- benign: nevi, solar lentigo, seborrheic keratosis
- malignant: pigmented BCC

Management

- excisional biopsy preferable, otherwise incisional biopsy
- remove full depth of dermis and extend beyond edges of lesion only after histologic diagnosis
- beware of lesions that regress – tumour is usually deeper than anticipated
- lymph node dissection shows survival advantage if nodes uninvolved
- chemotherapy (cis-platinum, BCG), high dose interferon for stage II (regional) and stage III (distant) disease
- radiotherapy may be used as adjunctive treatment

Table 23. American Joint Committee on Cancer Staging System Based on Breslow's Thickness of Invasion

T1 <1.0 mm	Stage I T1a - T2a	5-year survival 90%
T2 1.01-2.0 mm	Stage II T2b - T4b	5-year survival 70%
T3 2.01-4.0 mm	Stage III any nodes	5-year survival 45%
T4 >4.0 mm	Stage IV any mets	5-year survival 10%

a = no ulceration; b = ulceration



Risk Factors for Melanoma

no SPF is a SIN

Sun exposure

Pigment traits (blue eyes, fair/red hair, pale complexion)

Freckling

Skin reaction to sunlight (increased incidence of sunburn)

Immunosuppressive states (e.g. renal transplantation)

Nevi (dysplastic nevi; increased number of benign melanocytic nevi)



Node Dissection for Lesions > 10 mm

- Assess sentinel nodes
- If macroscopically or microscopically positive, a lymph node dissection should be performed prior to wide excision of the primary melanoma to ensure accurate lymphatic mapping.

Squamous Cell Carcinoma (SCC)



Clinical Presentation

- indurated erythematous nodule/plaque with surface scale/crust, and eventual ulceration
- more rapid enlargement than BCC
- sites: face, ears, scalp, forearms, dorsum of hands

Pathophysiology

- malignant neoplasm of keratinocytes (primarily vertical growth)
- predisposing factors include: UV radiation, PUVA, ionizing radiation therapy/exposure, chemical carcinogens (such as arsenic, tar and nitrogen mustards), HPV 16, 18, immunosuppression

Epidemiology

- second most common type
- primarily on sun-exposed skin in the elderly, M>F, skin phototypes I and II, chronic sun exposure
- in organ transplant recipients SCC is most common cutaneous malignancy, with increased mortality

Differential Diagnosis

- benign: nummular eczema, psoriasis, irritated seborrheic keratosis
- malignant: keratoacanthoma, Bowen's disease, BCC

Management

- surgical excision with primary closure, skin flaps or grafting
- lifelong follow-up (more aggressive treatment than BCC)

Prognosis

- good prognostic factors: immediate treatment, negative margins, and small size of lesion
- SCCs that arise from actinic keratosis metastasize less frequently (~1%) than other SCCs (e.g. arising de novo in old burns) (2-5% of cases)
- overall control is 75% over 5 years, 5-10% metastasize

BOWEN'S DISEASE (SQUAMOUS CELL CARCINOMA IN SITU)**Clinical Presentation**

- erythematous plaque with a sharply demarcated red and scaly border
- often 1-3 cm in diameter and found on the skin and mucous membranes
- evolves to SCC in 10-20% of cutaneous lesions and >20% of mucosal lesions

Management

- same as for BCC
- biopsy required for diagnosis
- topical 5-fluorouracil (Efudex®) or imiquimod (Aldara®) used if extensive and as a tool to identify margins of poorly defined tumours
- shave excision with electrodesiccation and curettage



Alopecia (Hair Loss)

Hair Growth

- hair grows in a cyclic pattern that is defined in 3 stages
 1. growth stage = anagen phase
 2. resting stage = telogen phase
 3. degenerative stage = catagen phase
- total duration of the growth stage reflects the type and location of hair: eyebrow, eyelash, and axillary hairs have a short growth stage in relation to the resting stage
- growth of the hair follicles is also based on the hormonal response to testosterone and dihydrotestosterone (DHT): this response is genetically controlled

Non-Scarring (Non-Cicatricial) Alopecia

PHYSIOLOGICAL**Clinical Presentation**

- male-pattern alopecia (androgenic alopecia)
- fronto-temporal areas progressing to vertex, entire scalp may be bald

Pathophysiology

- action of testosterone on hair follicles

Epidemiology

- early 20's-30's (female androgenic alopecia is diffuse and occurs in 40's and 50's)

Management

- minoxidil (Rogaine®) lotion to reduce rate of loss/partial restoration
- spironolactone in women (anti-androgenic effects), cyproterone acetate (Diane-35®)
- finasteride (Propecia®) (5- α -reductase inhibitor) 1 mg/d in men
- hair transplant

PHYSICAL

- trichotillomania: impulse-control disorder characterized by compulsive hair pulling with irregular patches of hair loss, and with remaining hairs broken at varying lengths
- traumatic (e.g. tight "corn-row" braiding of hair)

**Hair Loss****TOP HAT**

Telogen effluvium, tinea capitis

Out of Fe, Zn

Physical – trichotillomania, "corn-row" braiding

Hormonal – hypothyroidism, androgenic

Autoimmune – SLE, alopecia areata

Toxins – heavy metals, anticoagulants, chemotherapy, Vit A, SSRIs

TELOGEN EFFLUVIUM**Clinical Presentation**

- uniform decrease in hair density secondary to an increased number of hairs in resting stage (telogen stage)

Pathophysiology

- precipitated by: malnutrition, Fe deficiency, thyroid dysfunction, post-partum/miscarriage, scalp diseases (seborrheic dermatitis, allergic contact dermatitis), medications (e.g. OCP), physical/mental stress, Fe deficiency
- hair loss typically occurs 2-4 month after exposure to precipitant
- regrowth occurs within a few months but may not be complete

ANAGEN EFFLUVIUM**Clinical Presentation**

- hair loss due to insult to hair follicle impairing its mitotic activity (growth stage)

Pathophysiology

- precipitated by chemotherapeutic agents (most common), other meds (bismuth, levodopa, colchicine, cyclosporine), exposure to chemicals (thallium, boron, arsenic)
- dose-dependent effect
- hair loss 7-14 days after single pulse of chemotherapy; most clinically apparent after 1-2 months
- reversible effect; follicles resume normal mitotic activity few weeks after agent stopped

ALOPECIA AREATA**Clinical Presentation**

- autoimmune disorder characterized by patches of complete hair loss localized to scalp, eyebrows, beard, eyelashes
- alopecia totalis – loss of all scalp hair and eyebrows
- alopecia universalis – loss of all body hair
- associated with dystrophic nail changes – fine stippling
- “exclamation mark” pattern (hairs fractured and have tapered shafts, i.e. looks like “!”)
- may be associated with pernicious anemia, vitiligo, thyroid disease, Addison’s disease
- spontaneous regrowth may occur within months of first attack (worse prognosis if young at age of onset and extensive loss)
- frequent recurrence often precipitated by emotional distress

Management

- generally unsatisfactory
- intralesional triamcinolone acetonide (corticosteroids) can be used for isolated patches
- UV or PUVA therapy
- immunomodulatory (diphencyprone)

Scarring (Cicatricial) Alopecia**Clinical Presentation**

- irreversible loss of hair follicles with fibrosis

Etiology

- physical: radiation, burns
- infections: fungal, bacterial, TB, leprosy, viral (herpes zoster)
- inflammatory
 - lichen planus (lichen planopilaris)
 - discoid lupus erythematosus (DLE) (note that SLE can cause an alopecia unrelated to discoid lupus lesions which are non-scarring)
 - morphea: “coup de sabre” with involvement of centre of scalp

Investigations

- biopsy from active border

Management

- infections: treat underlying infection
- inflammatory: DLE treated topical/intralesional steroid or antimalarial



Non-scarring alopecia: intact hair follicles on exam → biopsy not required.

Scarring alopecia: absent hair follicles on exam → biopsy required.

**DDx of Non-scarring (non-cicatricial) Alopecia**

Alopecia

- Autoimmune
 - Alopecia areata
- Endocrine
 - Hypothyroidism
 - Androgens
- Micronutrient deficiencies
 - Iron
 - Zinc
- Toxins
 - Heavy metals
 - Anticoagulants
 - Chemotherapy
 - Vitamin A
- Trauma to the hair follicle
 - Trichotillomania
 - ‘Corn-row’ braiding
- Other
 - Severe illness
 - Childbirth

**DDx of Scarring (cicatricial) Alopecia**

Developmental/Hereditary Disorders

- Aplasia cutis congenita
- Epidermal nevi
- Romberg’s syndrome
- Generalized follicular hamartoma

Primary causes

- Group 1: Lymphocytic
 - Lupus erythematosus
 - Lichen planopilaris
 - Classic Pseudopelade
- Group 2: Neutrophilic
 - Folliculitis decalvans
- Group 3: Mixed
 - Acne keloidalis nuchae

Secondary causes

- Infectious agents
 - Bacterial (i.e. post-cellulitis)
 - Fungal (i.e. tinea capitis)
- Neoplasms (i.e. BCC, SCC, Lymphomas, and metastatic tumours)
- Physical agents
 - Mechanical trauma
 - Burns
 - Radiotherapy
 - Caustic chemicals



Nails and Disorders of the Nail Apparatus

Table 24. Nail Changes in Systemic and Dermatological Conditions

Nail Abnormality	Definition/Etiology	Associated Disease
NAIL PLATE CHANGES		
Clubbing	Proximal nail plate has greater than 180 degree angle to nail fold, watch-glass nails, bulbous digits	Cyanotic heart disease, bacterial endocarditis, pulmonary disorders, GI disorders, etc.
Koilonychia	Spoon shaped nails	Iron deficiency, malnutrition, diabetes
Onycholysis	Separation of nail plate from nail bed	Psoriasis, dermatophytes, thyroid disease
Onychogryphosis	Hypertrophy of the nail plate and subungal hyperkeratosis	Poor circulation, chronic inflammation, tinea
Onychohemia	Subungual hematoma	Trauma to nail bed
Onychomycosis	Fungal infection of nail (e.g. dermatophyte, yeast, mould)	HIV, diabetes, peripheral arterial disease
Onychocryptosis (Ingrown toenail)	Often hallux with congenital malalignment, painful inflammation, granulation tissue	Tight fitting shoes, excessive nail clipping
SURFACE CHANGES		
Wedge shaped	Distal margin has v-shaped indentation	Darier's disease (follicular dyskeratosis)
Pterygium inversus unguis	Distal nail plate does not separate from underlying nail bed	Scleroderma
Pitting	Punctate depressions that migrate distally with growth	Psoriasis, alopecia areata, eczema
Transverse ridging	Transverse depressions often more in central portion of nail plate	Serious acute illness slows nail growth (Beau's lines), eczema, chronic paronychia, trauma
Transverse white lines	Bands of white discolouration	Poisons, hypoalbuminemia (Muherke's lines)
COLOUR CHANGES		
Yellow		Tinea, jaundice, tetracycline, pityriasis rubra pilaris, yellow nail syndrome
Green		Pseudomonas
Black		Melanoma, hematoma
Brown		Nicotine use, psoriasis, poisons
Splinter hemorrhages	Extravasation of blood from longitudinal vessels of nail bed Blood attaches to overlying nail plate and moves distally as it grows	Trauma, bacterial endocarditis, blood dyscrasias, psoriasis
Oil spots	Brown-yellow discolouration	Psoriasis
NAIL FOLD CHANGES		
Herpetic whitlow	HSV infection of distal phalanx	Genital herpes infection
Paronychia	Local inflammation of the nail fold around the nail bed	Acute: painful infection Chronic: constant wetting (e.g. dishwashing, thumbsucking)
Nail fold telangiectasias	Cuticular hemorrhages, roughness, capillary changes	Scleroderma, SLE

Skin Manifestations of Systemic Disease



Table 25. Skin Manifestations of Internal Conditions

Disease	Related Dermatoses
AUTOIMMUNE DISORDERS	
Behçet's disease	Painful aphthous ulcers in oral cavity ± genital mucous membranes, erythema nodosum
Buerger's disease	Superficial migratory thrombophlebitis, pallor, cyanosis, gangrene, ulcerations
Dermatomyositis	Periorbital and perioral violaceous erythema, heliotrope with edema, Gottron's papules (violaceous flat-topped papules with atrophy), periungual erythema, telangiectasia, calcinosis cutis
Polyarteritis nodosa	Polyarteritic nodules, stellate purpura, erythema, gangrene, splinter hemorrhages, livedo reticularis
Rheumatic fever	Petechiae, urticaria, erythema nodosum, rheumatic nodules
Scleroderma	Raynaud's, nonpitting edema, waxy/shiny/tense atrophic skin (morphea), ulcers, cutaneous calcification, periungual telangiectasia, acrosclerosis
Systemic lupus erythematosus	Malar erythema, discoid rash (erythematous papules or plaques with keratotic scale, follicular plugging, atrophic scarring on face, hands, and arms), hemorrhagic bullae, palpable purpura, urticarial purpura, patchy/diffuse alopecia, mucosal ulcers, photosensitivity
Ulcerative colitis (UC)	Pyoderma gangrenosum, erythema nodosum
ENDOCRINE DISORDERS	
Addison's disease	Generalized hyperpigmentation or limited to skin folds, buccal mucosa and scars
Cushing's syndrome	Moon facies, purple striae, acne, hyperpigmentation, hirsutism, atrophic skin with telangiectasia
Diabetes mellitus	Infections (boils, carbuncles, candidiasis, <i>S. aureus</i> , dermatophytoses, tinea pedis and cruris, infectious eczematoid dermatitis), pruritus, eruptive xanthomas, necrobiosis lipidica diabetorum, granuloma annulare, diabetic foot, diabetic bullae, acanthosis nigricans, calciphylaxis
Hyperthyroidism	Moist, warm skin, seborrhea, acne, nail atrophy, hyperpigmentation, toxic alopecia, pretibial myxedema, acropachy, onycholysis
Hypothyroidism	Cool, dry, scaly, thickened, hyperpigmented skin; toxic alopecia with dry, coarse hair, brittle nails, myxedema, loss of lateral 1/3 eyebrows
HIV-RELATED	
Infections	Viral (HSV, HZV, HPV, cytomegalovirus, molluscum contagiosum, oral hairy leukoplakia), bacterial (impetigo, acneiform folliculitis, dental caries, cellulitis, bacillary epithelioid angiomatosis, syphilis), other (candidiasis)
Inflammatory dermatoses	Seborrhea, psoriasis, pityriasis rosea, vasculitis
Malignancies	Kaposi's sarcoma, lymphoma, BCC, SCC, malignant melanoma
MALIGNANCY	
Adenocarcinoma	
Gastrointestinal (GI)	Peutz-Jeghers: pigmented macules on lips/oral mucosa
Cervix/anus/rectum	Paget's Disease: eroding scaling plaques of perineum
Carcinoma	
Breast	Paget's Disease: eczematous and crusting lesions of breast
GI	Palmoplantar keratoderma: thickened skin of palms/soles
Thyroid	Sipple's Syndrome: multiple mucosal neuromas
Breast/GU/lung/ovary	Dermatomyositis: heliotrope erythema of eyelids and purplish plaques over knuckles
Lymphoma/Leukemia	
Hodgkin's	Ataxia Telangiectasia: telangiectasia on pinna, bulbar conjunctiva
Acute Leukemia	Ichthyosis: generalized scaling especially on extremities
	Bloom's syndrome: butterfly erythema on face, associated with short stature
Multiple Myeloma	Amyloidosis: large, smooth tongue with waxy papules on eyelids, nasolabial folds and lips, as well as facial petechiae
OTHERS	
Liver disease	Pruritus, hyperpigmentation, spider nevi, palmar erythema, white nails (Terry's nails), porphyria cutanea tarda, xanthomas, hair loss
Renal disease	Pruritus, pigmentation, half and half nails
Pruritic urticaria papules and plaques of pregnancy	Erythematous papules or urticarial plaques in distribution of striae distensae: buttocks, thighs, upper inner arms and lower backs
Cryoglobulinemia	Palpable purpura in cold-exposed areas, Raynaud's, cold urticaria, acral hemorrhagic necrosis, bleeding disorders, associated with hepatitis C infection



Raynaud's Phenomenon DDx

COLD HAND

Cryoglobulins/Cryofibrinogens
Obstruction/Occupational
Lupus erythematosus, other connective tissue disease
Diabetes mellitus/Drugs
Hematologic problems (polycythemia, leukemia, etc)
Arterial problems (atherosclerosis)
Neurologic problems (vascular tone)
Disease of unknown origin (idiopathic)



Acanthosis Nigricans

An asymptomatic dark thickened velvety hyperpigmentation of flexural skin most commonly around the neck. Associated with diabetes, obesity and other endocrine disorders and malignancy. It is a cutaneous marker of tissue insulin resistance.



Pediatric Exanthems



Itchy Eruptions in Childhood

UC-SCAB

Urticaria
Contact dermatitis
Scabies
Chicken pox
Atopic dermatitis
Bites

Definitions

- exanthem: an eruption on the skin occurring as a symptom of a systemic disease typically with a fever
- enanthem: an eruption on a mucous membrane occurring in the context of an exanthem

Table 26. Common Pediatric Exanthems

Exanthem	Etiology	Clinical Description	Important Complications	Management
Chicken Pox	Human herpes virus (HHV) 3 Incubation 10-21d, Communicable 1-2d Pre-rash to 5d post-rash	Diffuse vesicular pustular eruption beginning on thorax spreading to extremities New lesions every 2-3d Enanthems	Necrotizing fasciitis, encephalitis, cerebellar ataxia, disseminated intravascular coagulation (DIC), hepatitis	Supportive therapy, Acyclovir if severe, Varicella Zoster immunoglobulin (within 96 hrs of contact), Varicella vaccine
Enteroviral	Enteroviruses Most common exanthem in summer and fall	Polymorphous rash (macules, papules, vesicles, petechiae, urticaria)	None	Supportive care for majority Serious cases (immunosuppressed) can be treated with pleconaril
Erythema Infectiosum	Parvovirus B19 Incubation 4-14d Peaks in winter and spring	Slapped cheeks (red, flushed cheeks) then 1-4 days later lacy/reticular maculo-papular rash of trunk/extremities	STAR complex (Sore Throat, Arthritis, Rash) Fetal infection (anemia, fetal hydrops or death) Aplastic crisis in sickle cell patients	No treatment: children often feel well NSAIDs for symptomatic arthropathy
Gianotti-Crosti Syndrome	Epstein-Barr virus most common, hepatitis B, coxsackie, parvovirus Spring and early summer	Symmetric papular eruption of face, buttocks, and extremities	None	Supportive treatment
Hand, Foot and Mouth Disease	Coxsackie A and B viruses Highly contagious virus	Vesicular eruption of palms and soles with an erosive stomatitis	Pulmonary, neurological death	Supportive treatment
Kawasaki Disease	No proven viral etiology, but infectious etiology suggested Superantigen toxin-mediated bacterial process proposed Late winter to early spring	Fever >5 days and 4/5: unilateral lymphadenopathy; puffy/red palms and soles; red, cracked lips/strawberry tongue; skin rash; non-purulent bilateral conjunctivitis	Most common cause of vasculitis and acquired heart disease in children CNS, GI tract, kidney, eyes	Aspirin, intravenous immunoglobulin, baseline echo and repeat in 6 weeks
Measles	Paramyxovirus Incubation 10-14d Communicable 4d before and after rash	Erythematous macular eruption beginning on head and spreading downwards, desquamates, no palm or sole involvement Enanthem: Koplik spots (grey/white papules on buccal mucosa)	Otitis media, pneumonia, encephalitis, SJS, glomerular nephritis, myocarditis/pericarditis	Vitamin A, immunoglobulin, measles/mumps/rubella (MMR) vaccine
Roseola	HHV 6, HHV 7 Incubation 9-10d	Pink macules and papules on trunk, neck, proximal extremities, and occasionally face Eruption after high fever ends	Neurological involvement Viral reactivation in immunosuppressed patients	Supportive treatment Antipyretics during the febrile period
Rubella	RNA virus of the Togaviridae family Incubation 16-18d	1-5 days following mild prodrome (fever, headache, respiratory symptoms), a pink maculo-papular rash erupts on face spreading in a cephalocaudal direction Occipital and retroauricular nodes	STAR complex Congenital rubella (cataract, glaucoma, thrombocytopenia, hepatitis, deafness, congenital heart disease)	Supportive treatment MMR vaccine Serologic testing in rubella-exposed pregnant women
Scarlet Fever	Group A beta-hemolytic streptococci toxin types A, B, and C Late fall, winter, and early spring	Generalized rash, red papules, "sand-paper" texture, desquamation, flexural accentuation, enanthem (strawberry tongue, petechiae on palate) Pastia's lines – linear petechial streaks in axillary, inguinal, and antecubital areas	Mastoiditis, otitis, sinusitis, pneumonia, meningitis, myocarditis, arthritis, hepatitis, rheumatic fever, and glomerulonephritis	10-14 day course of penicillin

Miscellaneous Lesions

Angioedema and Urticaria

Angioedema

- deeper swelling of the skin involving subcutaneous tissues; often involves the eyes, lips, and tongue
- may or may not accompany urticaria
- hereditary or acquired forms
- hereditary angioedema (does not occur with urticaria)
 - onset in childhood; 80% have positive family history
 - recurrent attacks; 25% die from laryngeal edema
 - triggers: minor trauma, emotional upset, temperature changes
- treatment
 - prophylaxis with danazol or stanozolol
 - epinephrine pen to temporize until patient reaches hospital in acute attack

Urticaria

- also known as “Hives”; see Table 27 for classification
- transient, red, pruritic well-demarcated wheals
- each individual lesion lasts less than 24 hours
- second most common type of drug reaction
- results from release of histamine from mast cells in dermis
- can also result after physical contact with allergen

Table 27. Classification of Urticaria

Type	Approach to Diagnosis
Acute Urticaria >2/3 of cases Attacks last <6 weeks Individual lesions last <24 hrs	Drugs – especially aspirin, NSAIDs Foods – nuts, shellfish, eggs, fruit Idiopathic Infection Insect stings Percutaneous absorption – cosmetics, work exposures Stress Systemic diseases – systemic lupus erythematosus (SLE), endocrinopathy, neoplasm
Chronic Urticaria <1/3 of cases Attacks last >6 weeks Individual lesion lasts <24 hrs	IgE-dependent: trigger associated Idiopathic (90% of chronic urticaria patients) Aeroallergens Drugs (antibiotics, hormones, local anesthetics) Foods and additives Insect stings (bees, wasps, hornets) Parasitic infections Physical contact (animal saliva, plant resins, latex, metals, lotions, soap) Direct mast cell release Opiates, muscle relaxants, radio-contrast agents Complement-mediated Serum sickness, transfusion reactions Infections, viral/bacterial (>80% of urticaria in pediatric patients) Urticarial vasculitis Arachidonic acid metabolism ASA, NSAIDs Physical Dermatographism (friction, rubbing skin), cold (ice cube, cold water), cholinergic (hot shower, exercise), solar, pressure (shoulder strap, buttocks), aquagenic (exposure to water), adrenergic (stress), heat Other Mastocytosis, urticaria pigmentosa
Vasculitic Urticaria Individual lesions last >24 hrs Painful, non-pruritic Requires biopsy	Idiopathic Infections Hepatitis Autoimmune diseases SLE Drug hypersensitivity cimetidine and diltiazem



Wheal

- Typically erythematous flat-topped, palpable lesions varying in size with circumscribed dermal edema
- Individual lesion lasts <24 hrs
- Associated with mast cell release of histamine
- May be pruritic



DDx for Urticaria

DAM HIVES

- Drugs and foods
- Allergic
- Malignancy
- Hereditary
- Infection
- Vasculitis
- Emotions
- Stings



Approach to Urticaria

1. Thorough Hx and P/E
2. **Acute:** if individual lesions last <24 hours, but attacks last <6 weeks; no immediate investigations needed; consider referral for allergy testing
3. **Chronic:** if individual lesions last <24 hours but attacks last >6 weeks; further investigations required: CBC + diff, urinalysis, ESR, LFTs to help identify underlying cause
4. **Vasculitic:** if individual lesions last >24 hours; biopsy of lesion and referral to dermatology



Mastocytosis (Urticaria Pigmentosa)

Rare disease due to excessive infiltration of the skin by mast cells. It manifests as many reddish-brown elevated plaques and macules. Applying pressure to a lesion produces a wheal surrounded by intense erythema (Darier's sign), due to mast cell degranulation. This occurs within minutes.



Erythema Nodosum

Clinical Presentation

- acute or chronic inflammation of subcutaneous fat (panniculitis)
- round, red, tender, poorly demarcated nodules
- sites: asymmetrically arranged on lower legs, knees, arms
- associated with arthralgia, fever, malaise

Etiology

- 40% are idiopathic
- drugs: sulfonamides, oral contraceptives (also pregnancy), analgesics, trans retinoic acid
- infections: GAS, primary tuberculosis (TB), histoplasmosis, *Yersinia*
- inflammation: sarcoidosis, Crohn's > ulcerative colitis
- malignancy: acute leukemia, Hodgkin's lymphoma

Epidemiology

- 15-30 years old, F:M = 3:1
- lesions last for days and spontaneously resolve in 6 weeks

Investigations

- chest x-ray (to rule out chest infection and sarcoidosis)
- throat culture, antistreptolysin (ASO) titre, purified protein derivative (PPD) skin test

Management

- symptomatic: bed rest, compressive bandages, wet dressings
- NSAIDs
- treat underlying cause



DDx of Erythema Nodosum

NODOSUM

No cause (idiopathic) in 40%

Drugs (sulfonamides, OCP, etc.)

Other infections (GAS +)

Sarcoidosis

Ulcerative colitis and Crohn's

Malignancy (leukemia, Hodgkin's lymphoma)



Pruritus

Clinical Presentation

- a sensation provoking a desire to scratch
- pruritus can present with or without skin lesions
- lesions may arise from the underlying disease, or from excoriation causing crusts, lichenified plaques, or wheals

Etiology

- dermatologic – generalized
 - asteatotic dermatitis ("winter itch")
 - pruritus of senescent skin (may not have dry skin, any time of year)
 - infestations: scabies, lice
 - drug eruptions: ASA, antidepressants, opiates
 - psychogenic states
- dermatologic – local
 - atopic and contact dermatitis, lichen planus, urticaria, insect bites, dermatitis herpetiformis
 - infection: varicella, candidiasis
 - lichen simplex chronicus
 - prurigo nodularis
- systemic disease – usually generalized
 - hepatic: obstructive biliary disease, cholestatic liver disease of pregnancy
 - renal: chronic renal failure, uremia secondary to hemodialysis
 - hematologic: Hodgkin's lymphoma, multiple myeloma, leukemia, polycythemia vera, hemochromatosis, Fe deficiency anemia, cutaneous T-cell lymphoma
 - neoplastic: lung, breast, gastric (internal solid tumours)
 - endocrine: carcinoid, DM, hypothyroid/thyrotoxicosis
 - infectious: HIV, trichinosis, echinococcosis, hepatitis C
 - psychiatric: depression, psychosis
 - neurologic: post-herpetic neuralgia, multiple sclerosis

Investigations

- detailed history
- complete physical, including rectal and pelvic examination
- bloodwork: CBC, ESR, Cr/BUN, LFT, TSH, fasting blood sugar, stool culture and serology for parasites



DDx of Pruritus

SCRATCHED

Scabies

Cholestasis

Renal

Autoimmune

Tumours

Crazies (psychiatric)

Hematology (polycythemia, lymphoma)

Endocrine (thyroid, parathyroid, ↓ Fe)

Drugs, dry skin

Management

- treat underlying cause
- cool water compresses to relieve pruritus
- bath oil and emollient ointment (especially if xerosis is present)
- topical corticosteroid and antipruritics (e.g. menthol, camphor, phenol, mirtazapine, capsaicin)
- systemic antihistamines: H1 blockers are most effective, most useful for urticaria
- phototherapy with UVB or PUVA

Wounds and Ulcers**Table 28. Different Types of Ulcers and Treatment**

Ulcer Type	Clinical Presentation	Management
Arterial	Wound at tips of toes, cold feet with claudication, gangrene, distal hyperemia, decreased pedal pulses	Doppler study If ankle:brachial ratio <0.4, consider amputation If gangrenous, paint with betadine Otherwise, dressings to promote moist interactive wound healing
Venous	Wound at malleolus, stasis change, edema, previous venous injury	Local wound dressing: moist interactive healing Compression: preferably four layers After wound heals, support stockings for life
Neurotropic and Diabetic	Wound at pressure point or secondary to unknown trauma, common at base of 1st metatarsal phalangeal (MTP)	Pressure downloading by using proper shoes/seats Promote moist interactive wound healing Appropriate broad-spectrum antibiotic coverage
Vasculitic	Livedo reticularis, petechiae, extreme tenderness, delayed healing	Biopsy to determine vasculitis Serum screening for vasculitis Treat vasculitis Local moist interactive wound healing

**Uncommon Causes of Ulcers****CHIP IN**

Cancer, chromosomal
Hemoglobinopathy
Inflammatory
Pyoderma gangrenosum
Infections
Necrobiosis lipoidica diabetorum

**Key to a Wound that does Not Heal...**

- Relentless debridement of biofilm and antimicrobials
- Biopsy any wound without signs of healing after 3 months to rule out cancer!

Common Medications**Sunscreens and Preventative Therapy****Sunburn**

- erythema 2-6 hours post UV exposure often associated with edema, pain and blistering with subsequent desquamation of the dermis, and hyperpigmentation
- chronic UVB exposure leads to photoaging, immunosuppression, photocarcinogenesis
- prevention: avoid peak UVR (10 am to 4 pm), wear appropriate clothing, wide-brimmed hat, sunglasses, and broad-spectrum sunscreen
- clothing with UV protection expressed as UV protection factor (UPF) is analogous to SPF of sunscreen

Sunscreens

- sun protection factor (SPF): under ideal conditions an SPF of 10 means that a person who normally burns in 20 minutes will burn in 200 minutes following the application of the sunscreen
- topical chemical: absorbs UV light
 - requires application at least 15-60 minutes prior to exposure, should be reapplied every 2 hours (more often if sweating, swimming)
 - UVB absorbers: PABA, salicylates, cinnamates, benzylidene camphor derivatives
 - UVA absorbers: benzophenones, anthranilates, dibenzoylmethanes, benzylidene camphor derivatives
- topical physical: reflects and scatters UV light
 - titanium dioxide, zinc oxide, kaolin, talc, ferric chloride and melanin
 - ♦ all are effective against the UVA and UVB spectrum
 - less risk of sensitization than chemical sunscreens and waterproof, but may cause folliculitis or miliaria
- some sunscreen ingredients may cause contact or photocontact allergic reactions, but are uncommon

Management

- sunburn: if significant blistering present, consider treatment in hospital; otherwise, symptomatic treatment (cool wet compresses, oral anti-inflammatory, topical corticosteroids)
- antioxidants, both oral and topical are being studied for their abilities to protect the skin; topical agents are limited by their ability to penetrate the skin



SPF = burn time with cream/burn time without cream

**UV Radiation****UVA (320-400 nm): Aging**

- Penetrates skin more effectively than UVB or UVC
- Responsible for tanning, burning, wrinkling and premature skin aging
- Penetrates clouds, glass and is reflected off water, snow and cement

UVB (290-320 nm): Burning

- Absorbed by the outer dermis
- Is mainly responsible for burning and premature skin aging
- Primarily responsible for BCC, SCC
- Does not penetrate glass and is substantially absorbed by ozone

UVC (200-290 nm)

- Is filtered by ozone layer



Topical Steroids

Table 29. Potency Ranking of Topical Steroids

Relative Potency	Relative Strength	Generic Names	Trade Names	Usage
Weak	x1	hydrocortisone 1%	Emo Cort®	Intertriginous areas, children, face, thin skin
Moderate	x3	hydrocortisone 2% 17-valerate – 0.2% desonide mometasone furoate	Westcort® Tridesilon® Elocom®	Arm, leg, trunk
Potent	x6	betamethasone – 0.1% 17-valerate – 0.1% amcinonide	Betnovate® Celestoderm – V® Cyclocort®	Body
Very Potent	x9	betamethasone dipropionate – 0.05% fluocinonide – 0.05%	Diprosone® Lidex, Topsyn gel® Lyderm®	Palms and soles
Extremely Potent	x12	clobetasol propionate (most potent) betamethasone dipropionate ointment halobetasol propionate	Dermovate® Diprolene® Ultravate®	Palms and soles



Body Site: Relative Percutaneous Absorption

Forearm	1.0
Plantar foot	0.14
Palm	0.83
Back	1.7
Scalp	3.7
Forehead	6.0
Cheeks	13.0
Scrotum	42.0

Calculation of strength of steroid compared to hydrocortisone on forearm: relative strength of steroid x relative percutaneous absorption



Side Effects of Topical Steroids

- Local: Atrophy
Perioral dermatitis
Steroid acne
Rosacea
Contact dermatitis
Tachyphylaxis (tolerance)
- Systemic: Suppression of HPA axis

Dermatologic Therapies

Table 30. Topical Therapies that are Important in Dermatology

Drug Name	Dosing Schedule	Indications	Comments
Calcipotriol (Dovonex®)	0.005% cream, ointment, scalp solution, apply BID For maintenance therapy apply OD	Psoriasis	Burning, itching, skin irritation, worsening of psoriasis Avoid face, mucous membranes, eyes; wash hands after application Maximum weekly dosage of cream by age: 2-5 years – 25 g/wk 6-10 years – 50 g/wk 11-14 years – 75 g/wk > 14 years – 100 g/wk
Imiquimod (Aldara®)	5% cream applied 3x/wk Apply at bedtime, leave on 6-10 hours, then wash off with mild soap and water Max. duration 16 weeks	Genital warts Cutaneous warts Actinic keratosis Superficial basal cell carcinoma	Avoid natural/artificial sun exposure Local skin and application site reactions Erythema, ulceration, edema, flu-like symptoms Works best for warts on mucosal surfaces May induce inflammation and erosion
Permethrin (Kwellada® P Lotion and Nix® Dermal Cream)	5% cream, applied once overnight to all skin areas from neck down	Scabies (Kwellada-P Lotion, Nix® Dermal Cream) Pediculosis (Kwellada-P Crème Rinse®, Nix Crème Rinse®)	Do not use in children <2 yrs old Hypersensitivity to drug, or known sensitivity to chrysanthemums Local reactions only (resolve rapidly); including burning, pruritis Low toxicity, excellent results Consider 2nd application after 7 days
Pimecrolimus (Elidel®)	1.0% cream BID Use for as long as lesions persist and d/c upon resolution of symptoms	Atopic dermatitis (mild to moderate)	Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expensive
Tacrolimus topical (Protopic®)	0.03% (children) or 0.1% (adults) ointment BID Continue for duration of disease PLUS x 1 week after clearing	Atopic dermatitis (mild to moderate)	Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expensive



Vehicles

- Ointment (water in oil): hydrate, greasy
- Cream (oil in water): hydrate, variable
- Lotion (powder in water): drying, cosmesis
- Solutions (water, alcohol, propylene glycol)
- Gel (solution that melts on contact with skin): drying

Table 31. Oral Therapies that are Important in Dermatology

Drug Name	Dosing Schedule	Indications	Comments
Acitretin (Soriatane®)	25-50 mg PO OD; maximum 75 mg/d	Severe psoriasis Other disorders of hyperkeratinization (ichthyosis, Darier's disease)	<u>Monitoring strategies:</u> Monitor lipids, LFTs at baseline and q1-2wk until stable <u>Contraindications:</u> Women of childbearing potential unless strict contraceptive requirements are met <u>Drug interactions:</u> Other systemic retinoids, methotrexate, tetracyclines, certain contraceptives May be combined with PUVA phototherapy (known as re-PUVA)
Antivirals	famcyclovir (Famvir®) 250 mg PO TID x 7-10 days (for 1st episode of genital herpes) 125 mg PO BID x 5 d (for recurrent genital herpes) valacyclovir (Valtrex®) 1000 mg PO BID x 7-10 d (for 1st episode of genital herpes) 500 mg PO BID x 5 d (for recurrent genital herpes)	Chickenpox Herpes zoster Genital Herpes Acute and prophylactic to reduce transmission in infected patients Herpes labialis	<u>Side effects:</u> Headache, nausea, diarrhea, abdominal pain Reduce dose if impaired renal function <u>Side effects:</u> Dizziness, depression, abdominal pain Reduce dose if impaired renal function <u>Drug interactions:</u> cimetidine
Cyclosporin (Neoral®)	2.5-4 mg/kg/d PO div BID Max 4 mg/kg/d After 4 weeks may increase by 0.5 mg/kg/d q2wks Concomitant dose of magnesium may protect the kidneys	Psoriasis May also be effective in: Lichen Planus Dermatitis herpetiformis Erythema multiforme Recalcitrant urticaria Recalcitrant atopic dermatitis	<u>Monitoring strategies:</u> Blood pressure, renal function <u>Contraindications:</u> Abnormal renal function, uncontrolled hypertension, malignancy (except non-melanoma skin cancer), uncontrolled infection, immunodeficiency (excluding autoimmune disease), hypersensitivity to drug Long term effects preclude use of cyclosporin for >2 years; discontinue earlier if possible May consider rotating therapy with other drugs to minimize adverse effects of each drug
Dapsone	50-100-150 mg PO OD tapering to 25-50 mg PO OD to as low as 50 mg 2x/wk	Dermatitis herpetiformis	<u>Monitoring strategies:</u> Obtain G6PD levels before initiating; in the initial two weeks obtain methemoglobin levels and follow the blood counts carefully for the first few months <u>Side effects:</u> Neuropathy Hemolysis (Vitamin C and E supplementation can help prevent this) <u>Drug interactions:</u> Substrate of CYP2C8/9 (minor), 2C19 (minor), 2E1 (minor), 3A4 (major) Often a dramatic response within hours
Isotretinoin (Accutane®)	0.5-1 mg/kg/day given OD, to achieve a total dose of 120 mg/kg (i.e. 16-20 weeks)	Severe nodular and/or inflammatory acne Acne conglobata Recalcitrant acne	<u>Monitoring strategies:</u> Baseline lipid profile and hepatic enzymes before treatment, β-HCG <u>Contraindications:</u> Teratogenic – in females, reliable contraception is necessary Generally regarded as unsafe in lactation <u>Side effects:</u> Night blindness, decreased tolerance to contact lenses, dry mucous membranes May transiently exacerbate acne, dry skin Depression, myalgia <u>Drug interactions:</u> Do not use at the same time as tetracycline or minocycline – both may cause pseudotumour cerebri Discontinue vitamin A supplements Drug may be discontinued at 16-20 weeks when nodule count has dropped by >70%. A second course may be initiated after 2 months pm Refractory cases may require >3 courses
Itraconazole (Sporanox®)	100-400 mg PO OD, depending on infection treated Tinea corporis/cruris: 200 mg PO OD x 7 days Tinea pedis: 200 mg PO BID x 7 days Tinea versicolor: 200 mg PO OD x 7 days Toenails with or without fingernail involvement: 200 mg PO BID x 7 days once per month, repeated 3x Fingernail involvement only: 200 mg BID PO x 7 days once per month, repeated 2x	Onychomycosis Tinea corporis, cruris, pedis, versicolor, capitis	<u>Contraindications:</u> CHF <u>Side effects:</u> Serious hepatotoxicity <u>Drug Interactions:</u> Inhibits CYP 3A4. Increases concentration of some drugs metabolized by this enzyme Give capsules with food, capsules must be swallowed whole

Table 31. Oral Therapies that are Important in Dermatology (continued)

Drug Name	Dosing Schedule	Indications	Comments
Ivermectin (Mectizan [®] , Stromectol [®])	200-250 µg/kg PO qwkly x 2 Take once as directed; repeat one week later	Onchocerciasis (USA only) Not licensed for use in Canada Also effective for: Scabies	No significant serious side effects Efficacious
Methotrexate (Trexall [®])	10-25 mg qwk, PO, IM, or IV Max: 30 mg/wk To minimize side effects, consider folic acid supplementation: 1 mg to 5 mg 6 days/week	Psoriasis Atopic dermatitis Lymphomatoid papulosis May also be effective in: Cutaneous sarcoidosis	<u>Monitoring strategies:</u> Baseline renal, liver, and hematological studies <u>Contraindications:</u> Pregnancy, lactation, alcohol abuse, liver dysfunction, immunodeficiency syndrome, blood dyscrasias, hypersensitivity to drug Restricted to severe, recalcitrant or disabling psoriasis not adequately responsive to other forms of therapy May be combined with cyclosporine to allow lower doses of both drugs
Minocycline (Minocin [®])	50-100 mg PO BID Taper to 50 mg PO OD as acne lessens	Acne vulgaris Rosacea	<u>Contraindications:</u> Caution if impaired renal or liver function <u>Drug interactions:</u> Do not use with isotretinoin (Accutane [®]) <u>Side effects:</u> Extensive; affects multiple organ systems including CNS, teeth, eyes, bones, renal, and skin (photosensitivity, and blue pigmentation) Alternative to tetracycline
Terbinafine (Lamisil [®])	250 mg PO OD x 2 weeks Fingernails x 6 wks Toenails x 12 wks Confirm diagnosis prior to treatment	Onychomycosis Tinea corporis, cruris, pedis, capitis	<u>Contraindications:</u> Pregnancy, chronic or active liver disease <u>Drug interactions:</u> Potent inhibitor of CYP 2D6; use with caution when also taking beta-blockers, certain anti-arrhythmic agents, MAOI type B, and/or antipsychotics Drug concentrates rapidly in skin, hair and nails at levels associated with fungicidal activity
Tetracycline	250-500 mg PO daily Taken 1 hour before or 2 hours after a meal	Acne vulgaris Rosacea Bullous pemphigoid	<u>Contraindications:</u> Severe renal or hepatic dysfunction Pregnancy/lactation

References

Textbooks

- Bolognia JL, Jorizzo JL, Rapini RP, editors. Textbook of Dermatology. Vol. 1 and 2. Toronto: Mosby, 2003.
 Fitzpatrick JE and Aeling JL. Dermatology Secrets. 2nd ed. Philadelphia: Hanley & Belfus, 2001.
 Goodheart H, Goodheart's Photoguide to Common Skin Disorders: Diagnosis and management. 3rd Edition. Philadelphia: Lippincott, Williams and Wilkins, 2008
 Johnson RA, Suurmond D, Wolff K, editors. Colour atlas and synopsis of clinical dermatology. 5th ed. New York: McGraw Hill, 2005.
 Kraft J, Ng C, Bertucci V. University of Toronto Pharmacology Handbook: Dermatology Chapter. Toronto: publication pending.
 Lebwohl MG, Heymann WR, Berth-Jones J, Coulson I, editors. Treatment of skin disease: Comprehensive therapeutic strategies. 2nd ed. Philadelphia: Mosby, 2006.
 Paller AS, Mancini AJ. Hurwitz clinical pediatric dermatology: A textbook of skin disorders of childhood and adolescence. 3rd ed. China: Elsevier, 2006.
 Sterry W, Paus W, Burgdorf W editors. Thieme Clinical Companions: Dermatology. 5th ed, New York: Thieme, 2005.
 Wolff K, and Johnson RA, Fitzpatrick's Colour Atlas and Synopsis of Clinical Dermatology. 6th Edition. New York: McGraw Hill, 2009

Articles

- Cribier B et al. Erythema nodosum and associated diseases. Int J Dermatol. 1998;637-667.
 Cummings SR et al. Approaches to the prevention and control of skin cancer. Cancer Metastasis Rev. 1997;16:309.
 DeShazo RD et al. Allergic reactions to drugs and biologic agents. JAMA. 1997;278:1895.
 Ellis C, et al. ICCAD II Faculty. International Consensus Conference on Atopic Dermatitis II (ICCAD II): Clinical update and current treatment strategies. Br J Dermatol. 2003; 148 (suppl 63):3-10.
 Faergemann J, Baron R. Epidemiology, clinical presentation, and diagnosis of onychomycosis. Br J Dermatol. 2003; 149 (suppl 65):1-4.
 Friedmann PS. Assessment of urticaria and angio-edema. Clin Exper Allergy. 1999;29 (suppl 3):109.
 Gordon ML et al. Care of the skin at midlife: Diagnosis of pigmented lesions. Geriatrics. 1997;52:56-67.
 Krafchik, BR. Treatment of atopic dermatitis. J Cut Med Surg 3. 1999; 3(suppl 2):16-23.
 Mastrolorenzo A, Urbano FG, Salimbeni L, et al. Atypical molluscum contagiosum in an HIV-infected patient. Int J Dermatol. 1998; 27:378-380.
 Price VH. Treatment of hair loss. NEJM. 1999;341:964.
 Roujeau JC. Stevens-Johnson syndrome and toxic epidermal necrolysis are severe variants of the same disease which differs from erythema multiforme. J Dermatol. 1997;274-276.
 Walsh SRA and Shear NH. Psoriasis and the new biologic agents: Interrupting a T-AP dance. CMAJ. 2004;170(13):1933-1941.
 Whited JD et al. Does this patient have a mole or a melanoma? JAMA. 1998;279-676.
 Wilkin J, Dahl M, Detmar M, Drake L, Feinstein A, Odom R, Powell F. Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. J Amer Acad Dermatol. 2002;46(4):584-587.

Other Sources

- Canadian Dermatology Association 82nd Annual Conference. June 29-July 4, 2007. Toronto, Ontario, Canada.
 Pope E. Pediatric Exanthems. Lecture presentation to 2009-2010 University of Toronto Year 3 Medical Students.
<http://dermnetnz.org>

DM Diagnostic Medical Imaging

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Please see the Essentials of Medical Imaging software for illustrations of the content in this chapter

Imaging Modalities

X-Ray Imaging

Typical Effective Doses from Diagnostic Medical Exposures (in adults)*

Diagnostic Procedure	Equivalent Number of Chest x-rays	Approximate Equivalent Period of Natural Background Radiation** (~3 mSv/year)
X-ray examinations:		
Skull	5	12 days
Cervical spine	10	3 weeks
Thoracic spine	50	4 months
Lumbar spine	75	6 months
Chest (single PA film)	1	2 days
Shoulder	0.5	1 day
Mammography	20	7 weeks
Abdomen	35	3 months
Hip	35	3 months
Pelvis	30	10 weeks
Knee	0.25	<1 day
IVU	150	1 year
Dual x-ray absorptiometry (without/with CT)		
Upper GI series	0.5/2	<1 day/4 days
Small bowel series	300	2 years
Barium enema	250	20 months
	400	2.7 years
CT procedures:		
Head	100	8 months
Neck	150	1 year
Spine	300	2 years
Chest	350	2.3 years
Chest (pulmonary embolism)	750	5 years
Coronary angiography	800	5.3 years
Abdomen	400	2.7 years
Pelvis	300	2 years
Radionuclide studies:		
Brain (F-18 FDG)	705	4.7 years
Bone (Tc-99m)	315	2.1 years
Thyroid (Tc-99m)	240	1.6 years
Thyroid (I-123)	95	8 months
Cardiac rest-stress test		
(Tc-99m 1-day)	470	3 years
(Tc-99m 2-day)	640	4 years
Lung ventilation (Xe-133)	25	2 months
Lung perfusion (Tc-99m)	100	8 months
Renal (Tc-99m)	90 – 165	7 – 13 months
Liver-spleen (Tc-99m)	105	8.4 years
Biliary tract (Tc-99m)	155	1 year

*Source: *Radiology* 2008; 248(1):254-63.

**Calculated using average natural background exposure in Canada (Health Canada: <http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/environ/expos-eng.php>)

- x-rays, or Roentgen rays, are a form of electromagnetic energy of short wavelength
- as x-ray photons traverse matter, they can be absorbed (process known as “attenuation”) and/or scattered
- the density of a structure determines its ability to attenuate or “weaken” the x-ray beam
 - air < fat < water < bone < metal
- structures that have high attenuation, e.g. bone, appear white on the resulting images
- two broad categories: plain films and computed tomography (CT)

Plain Films

- x-rays pass through the patient and interact with a detection device to produce a 2-dimensional projection image
- structures closer to the film appear sharper and less magnified
- **contraindications:** pregnancy (relative)
- **advantages:** inexpensive, non-invasive, readily available
- **disadvantages:** radiation exposure, generally poor at distinguishing soft tissues

Computed Tomography (CT)

- x-ray beam opposite a detector moves in a continuous 360 degree arc as patient is advanced through the imaging system
 - subsequent computer assisted reconstruction of anatomical structures in the axial plane
- attenuation is quantified in Hounsfield units:
 - +1000 (bone) > +40 (muscle and soft tissue) > 0 (water) > -120 (fat) > -1000 (air)
- adjusting the “window width” (range of Hounsfield units displayed) and “window level” (midpoint value of the window width) can maximally visualize certain anatomical structures
 - e.g. CT chest can be viewed using “lung”, “soft tissue” and “bone” settings
- **contraindications:** pregnancy (relative), contraindications to contrast agents (e.g. renal failure)
- **advantages:** delineates surrounding soft tissues, excellent at delineating bones, excellent at identifying lung nodules/liver metastases, may be used to guide biopsies, spiral CT has fast data acquisition, helical CT allows 3D reconstruction, CT angiography is less invasive than conventional angiography
- **disadvantages:** high radiation exposure, IV contrast injection, anxiety of patient when going through scanner, higher cost than plain film, limited availability compared to plain films

Ultrasound (U/S)

- high frequency sound waves are transmitted from a transducer and passed through tissues; reflections of the sound waves are picked up by the transducer and transformed into images
- reflection (or “echo”) occurs when the sound waves pass through tissue interfaces of different acoustic densities
- structures are described based on their echogenicity; hyperechoic structures appear bright whereas hypoechoic structures appear dark on brightness-modulated images
- higher ultrasound frequencies result in greater resolution but greater attenuation (i.e. deeper structures more difficult to visualize)
- **artifacts:** acoustic shadowing refers to the loss of information below an interface (e.g. gallstone) that strongly reflects sound waves; enhancement refers to the increase in reflection amplitude from objects that lie below a weakly attenuating structure (e.g. cyst)
- **Doppler:** determines the velocity of blood flowing past the transducer based on the Doppler effect
- **Duplex scan:** Doppler + visual images
- **advantages:** relatively low cost, non-invasive, no radiation, real time imaging, may be used for guided biopsies, many different imaging planes (axial, sagittal), determines cystic versus solid
- **disadvantages:** highly operator-dependent, air in bowel may prevent imaging of midline structures in the abdomen, may be limited by patient habitus

Magnetic Resonance Imaging (MRI)

- non-invasive technique that does not use ionizing radiation
- able to produce images in virtually any plane
- patient is placed in a magnetic field; protons (H+) align themselves along the plane of magnetization due to intrinsic polarity. A pulsed radiofrequency beam is subsequently turned on which deflects all the protons off their aligned axes due to absorption of energy from the radiofrequency beam. When the radiofrequency beam is turned off, the protons return to their pre-excitation axis, giving off the energy they absorbed. This energy is measured with a detector and interpreted by a computer to generate MR images
- the MR image reflects the signal intensity as picked up by the receiver. This signal intensity is dependent on:
 1. hydrogen density: tissues with low hydrogen density (cortical bone, lung) generate little to no MR signal and appear black. Tissues with high hydrogen density (water) appear white on MRI
 2. magnetic relaxation times (T1 and T2): reflect quantitative alterations in MR signal strength due to intrinsic properties of the tissue and its surrounding chemical and physical environment (see Table 1)

Table 1. Signal Intensities in T1- and T2-weighted MR Imaging

Tissue or Body Fluid	T1-weighted	T2-weighted
Gas	Nil	Nil
Mineral-rich tissue (e.g. cortical bone, calculi)	Nil	Nil
Collagenous tissue (e.g. ligaments, tendons, scars)	Low	Low
Hemosiderin	Low	Low
Fat	High	Medium to high
Protein-containing fluid (e.g. abscess, complex cyst)	Medium	High
Synovium	Medium	High
Nucleus pulposus	Medium	High
High bound-water tissues	Low	Low to medium
Muscle, hyaline cartilage		
Liver, pancreas, adrenal		
High free-water tissues	Low	High
CSF, urine, bile, edema		
Simple cysts		
GU organs, including kidney		
Thyroid		
Hemorrhage		
Hyperacute (<24 hours); hyperacute venous hemorrhage is slightly less bright than arterial on T2 due to deoxyhemoglobin	Low-intermediate	High
Acute (1–6 days) reflects deoxyhemoglobin	Low-intermediate	Low
Chronic (>7 days) reflects methemoglobin		
Intracellular	High	Low
Extracellular	High	High
Late reflects hemosiderin	Low-intermediate	Low
Neuropathology	Low	High
Ischemia		
Edema		
Demyelination		
Most malignant tumours		
Meningioma	Medium / Isointense	Medium / Isointense



Remember that water is "white" on T2 as "World War II"

Positron Emission Tomography Scans (PET)

- non-invasive technique that involves exposure to ionizing radiation (~7 mSv)
- nuclear medicine imaging technique that produces images of functional processes in the body
- positron-producing radioisotope, such as 18-fluorodeoxyglucose (18-FDG) is chemically incorporated into a metabolically active molecule (glucose), injected into patient, travels to target organ, accumulates in tissues of interest, and radioactive substance begins to decay, sending off gamma rays which are detected by PET scanner
- **advantages:** shows metabolism and function of tissues (not only anatomic), allows oncologic diagnosis, staging, restaging (lung, breast, colorectal, lymphoma, melanoma, esophageal, head and neck), has oncologic predictive and prognostic value (breast, lymphoma), can evaluate cardiac viability
- **disadvantage:** cost, ionizing radiation, lack of anatomic reference (unless used with CT/MRI)
- **contraindications:** pregnancy

Contrast Enhancement

Contrast Agents in X-Ray Imaging

- contrast media are used to examine structures that do not have inherent contrast differences relative to their surroundings
- contrast can be administered by mouth (anterograde), rectum (retrograde) or intravenous injection prior to x-ray imaging
- contrast agents include barium sulphate (GI studies), iodine (intravenous pyelogram (IVP), endoscopic retrograde cholangio-pancreatography (ERCP), hysterosalpingography) and gas (air or CO₂ used in GI double contrast exams)

Table 2. Types of Contrast Routes

	Advantages	Disadvantages	Contraindications
Suppository (Barium Enema)	Delineates intraluminal anatomy, may demonstrate patency, lumen integrity, or large filling defects; under fluoroscopy, may also give information on function of an organ	Risk of contrast reaction; may cause renal failure in dehydrated patients with diabetes, myeloma or pre-existing renal disease	Previous adverse reaction to contrast, renal failure, multiple myeloma, dehydration, diabetes, severe heart failure; barium enema is also contraindicated in toxic megacolon, acute colitis, and suspected perforation (use Hypaque®)
IV Contrast	Same as above	Same as above	Previous adverse reaction to contrast, renal failure, multiple myeloma, dehydration, diabetes, severe heart failure



Acute Reactions to IV Contrast

Hot BUNS

Hypotension
Bradycardia
Urticaria
Nausea/vomiting
Seizures

Contrast Agents in MR Imaging

- gadolinium-chelates used to highlight the blood vessels or highly vascular structures (e.g. tumours)

Contrast Reactions

- contrast agents are generally safe; adverse reactions exist but they are uncommon
 - anaphylactoid reaction
 - contrast induced nephropathy
- treatment: diphenhydramine ± IV epinephrine

Chest Imaging

Chest X-Ray (CXR)

STANDARD VIEWS

- posteroanterior (PA):** patient stands erect with anterior chest against film plate to minimize distortion of the heart size
- lateral:** patient stands with arms above the head and left side against the film plate
 - better visualization of retrocardiac space and thoracic spine
 - more sensitive at picking up pleural effusions
 - helps localize lesions when combined with PA view
- anteroposterior (AP):** patient is supine with x-ray beam anterior
 - for bedridden patients (e.g. in ER, ICU or general ward)
 - enlarged cardiac silhouette and generally a lower quality film than PA
- lateral decubitus:** to assess for pleural effusion and pneumothorax in bedridden patients
- lordotic:** angled beam allowing better visualization of apices normally obscured by the clavicles and anterior ribs

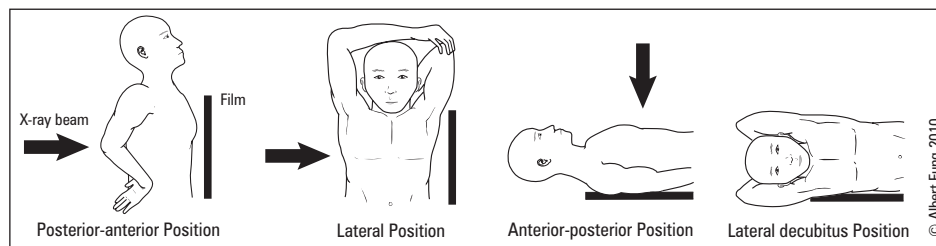


Figure 1. CXR Views

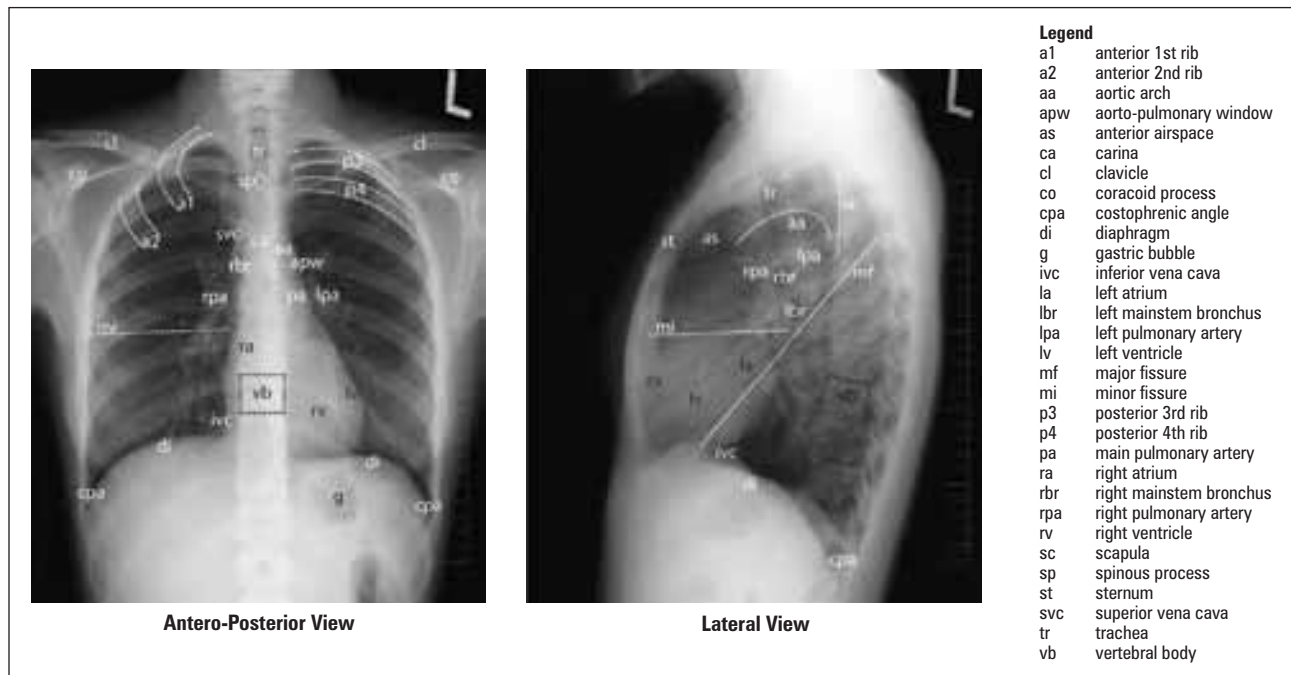


Figure 2. Location of Fissures, Mediastinal Structures and Bony Landmarks

ANATOMY

Localizing Lesions

- **silhouette sign:** loss of normal interfaces due to lung pathology (consolidation, atelectasis, mass), which can be used to localize disease in specific lung segments
 - note that pleural or mediastinal disease can also produce the silhouette sign

APPROACH TO CXR

Basics

- ID: patient name, MRN, sex, age
- date of exam
- markers: R and/or L
- technique: view (e.g. PA, AP, lateral), supine or erect
- indications for the study
- comparison: date of previous study for comparison (if available)
- quality of film: inspiration, penetration and rotation

Analysis

- **tubes and lines:** check position and be alert for pneumothorax or pneumomediastinum
- **soft tissues:** neck, axillae, pectoral muscles, breasts/nipples, chest wall
 - nipple markers can help identify nipples (may mimic lung nodules)
 - amount of soft tissue, presence of masses and air (subcutaneous emphysema)
- **abdomen** (see *GI imaging*, DM11):
 - free air under the diaphragm
 - air fluid levels, distention in small and large bowels
 - herniation of abdominal contents
- **bones:** C-spine, thoracic spine, shoulders, ribs, sternum
 - lytic and blastic lesions and fractures
- **mediastinum:** trachea, heart, great vessels, mediastinum, spine
 - cardiac enlargement, tracheal shift, tortuous aorta, widened mediastinum
- **hila:** pulmonary vessels, mainstem and segmental bronchi, lymph nodes
- **lungs:** lung parenchyma, pleura, diaphragm
 - lungs on lateral film should become darker when going inferiorly over the spine
 - comment on abnormal lung opacity, pleural effusions or thickening
 - right hemidiaphragm usually higher than left due to liver
 - right vs. left hemidiaphragm can be discerned on lateral CXR due to heart resting directly on left hemidiaphragm

Table 3. Localization Using the Silhouette Sign

Interface Lost	Location of Lung Pathology
Superior vena cava/ right superior mediastinum	RUL
Right heart border	RML
Right hemidiaphragm	RLL
Aortic knob/ left superior mediastinum	LUL
Left heart border	Lingula
Left hemidiaphragm	LLL



Chest X-Ray Interpretation

Basics ABCDEF

- AP, PA or other view
- Body position/rotation
- Confirm name
- Date
- Exposure/quality
- Films for comparison

Analysis ABCDEF

- Airways, and hilar Adenopathy
- Bones and Breast shadows
- Cardiac silhouette and Costophrenic angle
- Diaphragm and Digestive tract
- Edges of pleura
- Fields (lung fields)

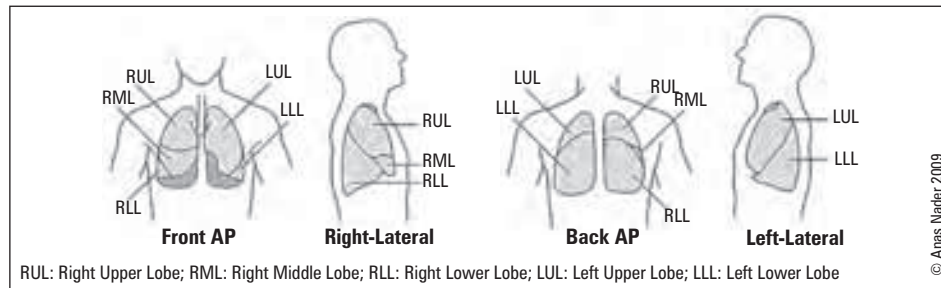


Figure 3. Location of Lobes of the Lung

Computed Tomography (CT) Chest

APPROACH TO CT CHEST

- **lung window**
 - central-trachea: patency, secretions
 - bronchial trees: anatomic variants, mucus plugs, airway collapse
 - lung parenchyma: fissures, nodules
- **bone window**
 - look at vertebrae, sternum, manubrium, ribs for fractures, lytic lesions, sclerosis
- **soft tissue window**
 - thyroid, chest wall, pleura
 - heart: chambers, coronary artery calcifications, pericardium
 - vessels: aorta, pulmonary artery, smaller vasculature
 - lymph nodes: mediastinal, axillary

TYPES OF CT CHEST

Table 4. Types of CT Chest

	Standard	High Resolution	Low Dose	CT Angiography
Advantage	Scans full lung very quickly (<1 minute)	Thinner slices provide high definition of lung parenchyma	1/5th the radiation	Iodinated contrast highlights vasculature
Disadvantage	Poor at evaluating diffuse disease	Only 5-10% lung is sampled	Decreased detail	Contrast can cause severe allergic reaction and is nephrotoxic
Contrast	±	No	No	Yes
Indication	CXR abnormality Pleural and mediastinal abnormality Lung cancer staging Follow up metastases Empyema vs. abscess	Hemoptysis Diffuse lung disease (e.g. sarcoidosis, hypersensitivity pneumonitis, pneumoconiosis) Pulmonary fibrosis Normal CXR but abnormal PFTs Characterize solitary pulmonary nodule	Screening Follow up infections, lung transplant, metastases	Pulmonary embolism Aortic aneurysms Aortic dissection

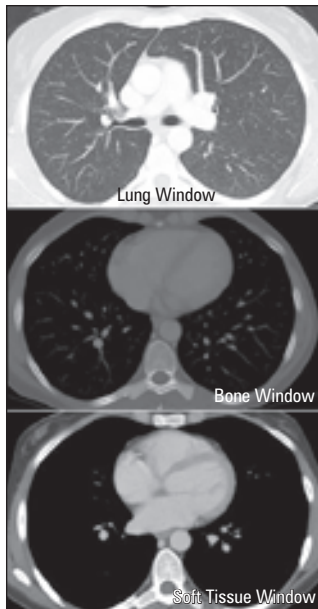


Figure 4. CT Thorax Windows

Lung Abnormalities

ATELECTASIS

- **pathophysiology:** collapse of alveoli due to restricted breathing, blockage of bronchi, external compression or poor surfactant
- **signs**
 - increased opacity of involved segment/lobe, silhouette sign
 - volume loss: fissure deviation, hilar/mediastinal displacement, diaphragm elevation
 - vascular crowding
 - compensatory hyperinflation of remaining normal lung
 - air bronchograms (also seen in consolidation)
- **differential**
 - **obstructive** (most common): air distal to obstruction is reabsorbed causing alveolar collapse
 - ♦ endobronchial lesion, foreign body, inflammation (granulomatous infections, pneumoconiosis, sarcoidosis, radiation injury) or mucous plug (seen in cystic fibrosis)
 - **compressive**
 - ♦ tumour, bulla, effusion, enlarged heart, lymphadenopathy
 - **traction (cicatrization):** due to scarring, which distorts alveoli and contracts the lung
 - **adhesive:** due to lack of surfactant
 - ♦ hyaline membrane disease, prematurity
 - **passive (relaxation):** a result of air or fluid in the pleural space
 - ♦ pleural effusion, pneumothorax
- **management:** in the absence of a known etiology, persisting atelectasis must be investigated (CT thorax) to rule out a bronchogenic carcinoma



DDx of Airspace Disease

- Pus (e.g. pneumonia)
- Fluid (e.g. pulmonary edema)
- Blood (e.g. pulmonary hemorrhage)
- Cells (e.g. bronchioalveolar carcinoma; lymphoma)
- Protein (e.g. alveolar proteinosis)



DDx of Interstitial Disease

- Pulmonary edema
- Collagen disease (e.g. fibrosis)
- Sarcoidosis
- Pneumoconiosis
- Metastatic disease (e.g. lymphangitic permeation)
- Inflammatory conditions (e.g. early viral pneumonia, interstitial pneumonia)

CONSOLIDATION

- **pathophysiology:** fluid (water, blood), inflammatory exudates, or tumour in alveoli
- **signs**
 - air bronchograms: lucent branching bronchi visible through opacification
 - airspace nodules: fluffy, patchy, poorly margined appearance with later tendency to coalesce, may take on lobar or segmental distribution
- **differential**
 - **fluid:** pulmonary edema, blood (trauma, vasculitis, bleeding disorder, pulmonary infarct)
 - **inflammatory exudates:** bacterial infections, TB, allergic hypersensitivity alveolitis, bronchiolitis obliterans organizing pneumonia (BOOP), allergic bronchopulmonary aspergillosis (ABPA), aspiration, sarcoidosis
 - **tumour:** bronchioalveolar carcinoma, lymphoma
- **management:** in the absence of a known etiology, persisting atelectasis must be investigated (CT thorax) to rule out a bronchogenic carcinoma

INTERSTITIAL DISEASE

- **pathophysiology:** pathological process involving the interlobular connective tissue (i.e. "scaffolding of the lung")
- **signs**
 - **linear:** fine lines caused by thickened connective tissue septae
 - ♦ Kerley A: long thin lines in upper lobes
 - ♦ Kerley B: short horizontal lines extending from lateral lung margin
 - ♦ Kerley C: diffuse linear pattern throughout lung
 - **nodular:** 1-5 mm well-defined nodules distributed evenly throughout lung
 - ♦ seen in malignancy, pneumoconiosis and with granulomas (sarcoidosis, miliary TB)
 - **reticular (honeycomb):** parenchyma replaced by thin-walled cysts suggesting extensive destruction of pulmonary tissue and fibrosis
 - ♦ seen in interstitial pulmonary fibrosis (IPF), asbestosis and CVD
 - ♦ NOTE: watch for pneumothorax as a complication
 - **reticulonodular:** combination of reticular and nodular patterns
 - may also see signs of airspace disease (atelectasis and consolidation)
- **differential**
 - occupational/environmental exposure
 - ♦ inorganic: asbestosis, coal miner's pneumoconiosis, silicosis, berylliosis, talc pneumoconiosis
 - ♦ organic: bird fancier's lung, farmer's lung (moldy hay)
 - autoimmune: CVD, IBD, celiac disease, vasculitis
 - drug-related: antibiotics (cephalosporins, nitrofurantoin), NSAIDs, phenytoin, carbamazepine, fluoxetine, chemotherapy, heroin, cocaine, methadone
 - idiopathic: hypersensitivity pneumonitis, IPF, BOOP
- **management**
 - high resolution CT thorax
 - biopsy

PULMONARY NODULE (see Table 5)

- **signs:** round opacity ± silhouette sign
 - note: do not mistake nipple shadows for nodules; if in doubt, repeat CXR with nipple markers
- **differential**
 - **extrapulmonary density:** nipple, skin lesion, electrode, pleural mass, bony lesion
 - **solitary nodule:**
 - ♦ tumour: carcinoma, hamartoma, metastasis, bronchial adenoma
 - ♦ inflammation: histoplasmosis, tuberculoma, coccidioidomycosis
 - ♦ vascular: AV fistula, pulmonary varix (dilated pulmonary vein), infarct, embolism
 - **multiple nodules:** metastases, abscess, granulomatous lung disease (TB, fungal, sarcoid, rheumatoid nodules, silicosis, Wegener's disease)
- **management**
 - clinical information and CT appearance determine level of suspicion of malignancy
 - ♦ if high probability, invasive testing (fine needle aspiration, transbronchial/transsthoracic biopsy) is indicated
 - ♦ if low probability, repeat CXR or CT in 1-3 months and then every 6 months for 2 years; if no change, then >99% chance benign

**DDx for Cavitating Lung Nodule****WEIRD HOLES**

Wegener's syndrome
 Embolic (pulmonary, septic)
 Infection (anaerobes, pneumocystis, TB)
 Rheumatoid (necrobiotic nodules)
 Developmental cysts (sequestration)
 Histiocytosis
 Oncological
 Lymphangioleiomyomatosis
 Environmental, occupational
 Sarcoidosis

Table 5. Characteristics of Benign and Malignant Pulmonary Nodules

	Malignant	Benign
Margin	Ill-defined/spiculated ("corona radiata")	Well-defined
Contour	Lobulated	Smooth
Calcification	Eccentric or stippled	Diffuse, central, popcorn, concentric
Doubling Time	20-460 days	<20 days or >460 days
Other Features	Cavitation, collapse, adenopathy, pleural effusion, lytic bone lesions, smoking history	
Size	>3 cm	<3 cm
Cavitation	Yes, especially with wall thickness >15 mm, eccentric cavity and shaggy internal margins	No
Satellite Lesions	No	Yes

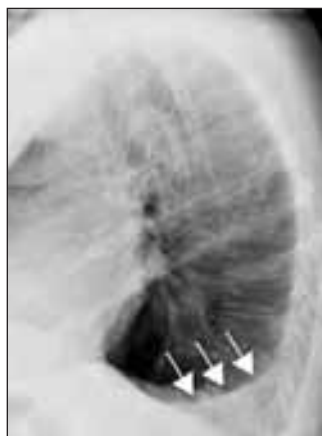


Figure 5. Pleural Effusion in Lateral View



Figure 6. Pneumothorax

**Elevated Hemidiaphragm Suggests:**

- Intra-abdominal process
- Pregnancy
- Diaphragmatic paralysis
- Atelectasis
- Lung resection
- Pneumonectomy

Pleural effusion also may result in apparent elevation.

Depressed Hemidiaphragm Suggests:

- Asthma
- COPD
- Large pleural effusion
- Tumour

Pulmonary Vascular Abnormalities

PULMONARY EDEMA

- **signs**
 - vascular redistribution/enlargement, pleural effusion, cardiomegaly (may be present in cardiogenic edema and fluid overloaded states)
 - edema fluid initially collects in interstitium:
 - ♦ loss of definition of pulmonary vasculature
 - ♦ peribronchial cuffing
 - ♦ Kerley B lines
 - ♦ reticulonodular pattern
 - ♦ thickening of interlobar fissures
 - as pulmonary edema progresses, fluid begins to collect in alveoli causing diffuse air space disease often in a "bat wing" or "butterfly" pattern in perihilar regions with tendency to spare the outermost lung fields
- **differential:** cardiogenic (CHF), renal failure, volume overload, non-cardiogenic (ARDS)

PULMONARY EMBOLISM

- **signs:** Westermark sign (localized pulmonary oligemia), Hampton's hump (triangular peripheral infarct), enlarged RV and RA, pulmonary edema, atelectasis, pleural effusion
- **management:** V/Q scan, CT angiography (look for filling defect)

Pleural Abnormalities

PLEURAL EFFUSION

Table 6. Sensitivity of Plain Film Views for Pleural Effusion

X-ray Projection	Minimum Volume to Visualize
Lateral decubitus	25 mL – most sensitive
Upright lateral	50 mL – meniscus seen in the posterior costophrenic sulcus
PA	200 mL
Supine	Diffuse haziness

- a horizontal fluid level is seen only in a hydropneumothorax (both fluid and air within pleural cavity)
- effusion may exert mass effect, shift trachea and mediastinum to opposite side, or cause atelectasis of adjacent lung
- U/S is superior to plain film for detection of small effusions and may also aid in thoracentesis

PNEUMOTHORAX

- **signs**
 - upright chest film allows visualization of visceral pleura as curvilinear line paralleling chest wall, separating partially collapsed lung from pleural air
 - more obvious on expiratory (increased contrast between lung and air) or lateral decubitus film (air collects superiorly)
 - more difficult to detect on supine film; look for the "deep (costophrenic) sulcus" sign, "double diaphragm" sign (dome and anterior portions of diaphragm outlined by lung and pleural air, respectively), hyperlucent hemithorax, sharpening of adjacent mediastinal structures
 - mediastinal shift may occur if air is under tension ("tension pneumothorax")
- **differential:** spontaneous (tall and thin males, smokers), iatrogenic (lung biopsy, ventilation, CVP line insertion), trauma (associated with rib fractures), emphysema, malignancy, honeycomb lung

ASBESTOS

- asbestos exposure may cause various pleural abnormalities including benign plaques (most common) that may calcify, diffuse pleural fibrosis, effusion, and malignant mesothelioma

Mediastinal Abnormalities**Mediastinal Mass**

- the mediastinum is divided into three compartments; this provides the approach to the differential diagnosis of a mediastinal mass
- anterior (anterior line formed by anterior trachea and posterior border of heart and great vessels)
 - **4 T's:** thyroid, thymic neoplasm (e.g. thymoma), teratoma, and "terrible" lymphoma
 - cardiophrenic angle mass differential: thymic cyst, epicardial fat pad, foramen of Morgagni hernia
- middle (extending behind anterior mediastinum to a line 1 cm posterior to the anterior border of the thoracic vertebral bodies)
 - esophageal carcinoma, esophageal duplication cyst
 - metastatic disease
 - lymphadenopathy (all causes)
 - hiatus hernia
 - bronchogenic cyst
- posterior (posterior to the middle line described above)
 - neurogenic tumour (e.g. neurofibroma, schwannoma)
 - multiple myeloma
 - pheochromocytoma
 - neuroenteric cyst, thoracic duct cyst
 - lateral meningocele
 - Bochdalek hernia
 - extramedullary hematopoiesis
- in addition, any compartment may give rise to lymphoma, lung cancer, aortic aneurysm or other vascular abnormalities, abscess, and hematoma

**DDx Anterior Mediastinal Mass****4 Ts**

Thyroid
Thymus
Teratoma
"Terrible" lymphoma

**DDx of Increased Cardiothoracic Ratio**

- Cardiomegaly (myocardial dilatation or hypertrophy)
- Pericardial effusion
- Poor inspiratory effort/low lung volumes
- Pectus excavatum

ENLARGED CARDIAC SILHOUETTE

- heart borders
 - on PA view, right heart border is formed by right atrium; left heart border is formed by left atrium and left ventricle
 - on lateral view, anterior heart border is formed by right ventricle; posterior border is formed by left atrium (superior to left ventricle) and left ventricle
- cardiothoracic ratio = greatest transverse dimension of the central shadow relative to the greatest transverse dimension of the thoracic cavity
 - in an adult, good quality erect PA chest film, cardiothoracic ratio of >0.5 is abnormal
 - differential of ratio >0.5
 - ♦ cardiomegaly (myocardial dilatation or hypertrophy)
 - ♦ pericardial effusion
 - ♦ poor inspiratory effort/low lung volumes
 - ♦ pectus excavatum
 - ratio <0.5 does not exclude enlargement (e.g. cardiomegaly + concomitant hyperinflation)
- pericardial effusion
 - globular heart
 - loss of indentations on left mediastinal border
 - peri- and epicardial fat pad separation on lateral film ("sandwich sign")
- right atrial enlargement
 - increase in curvature of right heart border
 - enlargement of SVC
- left atrial enlargement
 - straightening of left heart border
 - increased opacity of lower right side of cardiovascular shadow (double heart border)
 - elevation of left main bronchus (specifically, the upper lobe bronchus on the lateral film), distance between left main bronchus and "double" heart border >7 cm, splayed carina (late sign)
- right ventricular enlargement
 - elevation of cardiac apex from diaphragm
 - anterior enlargement leading to loss of retrosternal air space on lateral
 - increased contact of RV against sternum
- left ventricular enlargement
 - displacement of cardiac apex inferiorly and posteriorly
 - "boot-shaped" heart
 - Rigler's sign: on lateral film, from junction of IVC and heart at level of the left hemidiaphragm, measure 1.8 cm posteriorly then 1.8 cm superiorly \rightarrow if cardiac shadow extends beyond this point, then LV enlargement is suggested
 - ♦ note: not to be confused with Rigler's sign in the abdomen

Tubes, Lines, and Catheters

- ensure appropriate placement and assess potential complications of lines and tubes
- avoid mistaking a line/tube for pathology (e.g. oxygen rebreather mask for pneumothoraces)

Central Venous Catheter

- primarily used to administer fluids, medications, and vascular access for hemodialysis – also monitor central venous pressure (CVP)
- tip must be located distal to (above) right atrium as this prevents catheter from producing arrhythmias or perforating wall of atrium
 - if monitoring CVP – catheter tip must be proximal to venous valves
- tip of well positioned central venous catheter projects over silhouette of SVC in a zone demarcated superiorly by the anterior first rib end and clavicle and inferiorly by top of RA
- course should parallel course of SVC – if appears to bend as it approaches wall of SVC or appears perpendicular, catheter may damage and ultimately perforate wall of SVC
- **complications:** pneumothorax, bleeding (mediastinal, pleural), air embolism



Figure 7. Well Positioned Central Venous Catheter (CXR)

Endotracheal Tube

- frontal chest film: tube projects over trachea and shallow oblique or lateral chest radiograph will help determine position in 3 dimensions
- progressive gaseous distention of stomach on repeat imaging is concerning for esophageal intubation
- tip should be located 4 cm above tracheal carina – avoids selective intubation of right/left mainstem bronchus as patient moves, low enough so it does not rub against vocal chords
- tube should not be inflated to the point that it continuously and completely occludes tracheal lumen as it may cause pressure induced necrosis of tracheal mucosa and predispose to rupture or stenosis
- maximum inflation diameter <3 cm – ensure diameter of balloon is less than tracheal diameter above and below balloon
- **complications:** aspiration (parenchymal opacities), pharyngeal perforation (subcutaneous emphysema, pneumomediastinum, mediastinitis)

Nasogastric Tube (NG Tube)

- tip and sideport of NG tube should be positioned distal to esophagogastric junction and proximal to gastric pylorus
- radiographic confirmation of tube is mandatory because clinical techniques for assessing tip position may be unreliable
- **complications:** aspiration (parenchymal opacities), intracranial perforation (trauma patients), pneumothorax

Swan-Ganz Catheter

- to monitor pulmonary capillary wedge pressure and to measure cardiac output in patients suspected of having left ventricular dysfunction
- tip of Swan-Ganz catheter should be positioned within right or left main pulmonary arteries or in one of their large, lobar branches
- if tip is located more distally, increased risk of prolonged pulmonary artery occlusion resulting in pulmonary infarction or, rarely, pulmonary artery rupture
- **complications:** pneumothorax, bleeding (mediastinal, pleural), air embolism

Chest Tube

- ideally placed to evacuate gas or fluid from pleural space
- gas tends to collect in nondependent portion of pleural space, while fluid lies in dependent portion
- chest tube to evacuate fluid usually in dorsal and caudal portion of pleural space
 - for pneumothoraces: ventral and cephalad portions of pleural space
- tube may lie in fissure as long as clinically performing function
- **complications:** lung perforation (mediastinal opacities)

Gastrointestinal (GI) Tract

Modalities

Abdominal X-Ray (AXR)

- indications:
 - acute abdomen: bowel perforation, toxic megacolon, bowel ischemia, small bowel obstruction (SBO), large bowel obstruction (LBO)
 - chronic symptoms: constipation, calcifications (gallstones, renal stones, urinary bladder stones, etc.)
 - not useful in: GI bleed, chronic anemia, vague GI symptoms
- AXR – 3 most common views: supine, upright and left lateral decubitus (LLD)



3 Views of Abdomen

- Left lateral decubitus AXR
- Supine AXR
- Erect/Upright AXR

Table 7. Differentiating Small and Large Bowel

Property	Small Bowel	Large Bowel
Mucosal Folds	Uninterrupted valvulae conniventes (or plicae circularis)	Interrupted haustra extend only partway across lumen
Location	Central	Peripheral (picture frame)
Maximum diameter	3 cm	6 cm (9 cm at cecum)
Maximum fold thickness	3 mm	5 mm
Other	Rarely contains solid fecal material	Commonly contains solid fecal material

- abdomen divided into 2 cavities:
 - peritoneal cavity – lined by peritoneum that wraps around most of the bowel, the spleen, and most of the liver; forms a recess lateral to both the ascending and descending colon (paracolic gutters)
 - retroperitoneal cavity – contains duodenum (2nd, 3rd, and 4th parts), ascending and descending colon and the rectum, pancreas, kidneys, adrenal glands, ureters, bladder, psoas muscles, and the abdominal aorta; the contour of several of these organs can often be seen on radiographs



What's in the Retroperitoneum?

- Duodenum (2nd, 3rd, 4th part)
- Ascending, descending colon
- Rectum
- Kidneys, ureters, bladder, adrenals
- Psoas, quadratus lumborum
- Aorta, inferior vena cava

Abdominal CT

- plain CT: renal colic, hemorrhage
- contrast CT
 - IV contrast given immediately before or during CT to allow identification of arteries and veins
 - portal venous phase: indicated for majority of cases
 - biphasic (arterial and portal venous phases): liver, pancreas, bile duct tumours
 - oral contrast: barium or water soluble (water soluble if suspected perforation) given in most cases to demarcate GI tract
 - rectal contrast: given for investigation of colonic lesions
 - caution: contrast allergy (may premedicate with steroids and antihistamine)
 - contraindication: impaired renal function, based on eGFR

Approach to Abdominal X-Ray (AXR)

- mnemonic: “IT Free ABDO”
- I = identification:** date, name, MRN, age of patient, type of study
- T = technical factors:** good coverage, appropriate penetration, identify view
- Free = free fluid**
 - small amounts of fluid → increased distance between lateral fat stripes and adjacent colon may indicate free peritoneal fluid in the paracolic gutters
 - large amounts of fluid → diffuse increased opacification on supine film; bowel floats to centre of anterior abdominal wall
 - ascites and blood (hemoperitoneum) are the same density on the radiograph and therefore cannot be differentiated
- A = air**
 - volvulus (“twisting of the bowel upon itself”) – from most to least common:
 - sigmoid: “coffee bean” sign (massively dilated sigmoid projects to right or mid-upper abdomen) with proximal large bowel dilation
 - cecal: massively dilated bowel loop projecting to left or mid-upper abdomen with small bowel dilation
 - gastric: rare
 - small bowel: “corkscrew sign” (rarely diagnosed on plain films, seen best on CT)
 - toxic megacolon
 - manifestation of fulminant colitis
 - extreme dilatation of colon (>6.5 cm) with mucosal changes including foci of edema, ulceration and pseudopolyps, loss of normal haustral pattern



Approach to AXR

IT Free ABDO

- Identification
- Technical factors
- Free fluid
- Air
- Bowel wall thickening
- Densities (bones, calcifications)
- Organs

Table 8. Abnormal Air on Abdominal X-Ray

Air	Appearance	Common Etiologies
Extraluminal		
Intraperitoneal (pneumoperitoneum)	Upright film: air under diaphragm LLD film: air between liver and abdominal wall supine film: gas outlines of structures not normally seen: <ul style="list-style-type: none"> • Inner and outer bowel wall (Rigler's sign) • Falciform ligament • Peritoneal cavity ("football" sign) 	Perforated viscus Postoperative (up to 10 days to be resorbed)
Retroperitoneal	Gas outlining retroperitoneal structures allowing increased visualization: <ul style="list-style-type: none"> • Psoas shadows • Renal shadows 	Perforation of retroperitoneal segments of bowel: duodenal ulcer, post-colonoscopy
Intramural (pneumatosis intestinalis)	Lucent air streaks in bowel wall, 2 types: <ol style="list-style-type: none"> 1. Linear 2. Rounded (cystoides type) 	1. Linear: ischemia, necrotizing enterocolitis 2. Rounded/cystoides (generally benign): primary (idiopathic), secondary to COPD
Intraluminal	Dilated loops of bowel, air-fluid levels	Adynamic (paralytic) ileus, mechanical bowel obstruction (see Table 9)
Loculated	Mottled, localized in abnormal position without normal bowel features	Abscess (evaluate with CT)
Biliary	Air centrally over liver	Sphincterotomy, gallstone ileus, erosive peptic ulcer, cholangitis, emphysematous cholecystitis
Portal Venous	Air peripherally over liver in branching pattern	Bowel ischemia/infarction

**Biliary vs. Portal Venous Air**

"Go with the flow": air follows the flow of bile or portal venous blood.

Biliary air is most prominent centrally over the liver.

Portal venous air is most prominent peripherally.

Table 9. Adynamic Ileus vs. Mechanical Obstruction

Feature	Adynamic Ileus	Mechanical Obstruction
Calibre of Bowel Loops	Normal or dilated	Usually dilated
Air-Fluid Levels (erect and LLD films only)	Same level in a single loop	Multiple air fluid levels giving "step ladder" appearance, dynamic (indicating peristalsis present) "string of pearls" (row of small gas accumulations in the dilated valvulae conniventes)
Distribution of Bowel Gas	Air throughout GI tract generalized or localized <ul style="list-style-type: none"> • In a localized ileus (e.g. pancreatitis, appendicitis): dilated "sentinel loop" remains in the same location on serial films, usually adjacent to the area of inflammation 	Dilated bowel up to the point of obstruction (i.e. transition point) No air distal to obstructed segment "Hairpin" (180°) turns in bowel

- **B = bowel wall thickening**

- increased soft tissue density in bowel wall, thumb-like indentations in bowel wall ("thumb-printing"), or a picket-fence appearance of the valvulae conniventes ("stacked coin" appearance)
- may be seen in IBD, infection, ischemia, hypoproteinemic states, and submucosal hemorrhage

- **D = densities**

- bones – look for gross abnormalities of lower ribs, vertebral column, and bony pelvis
- abnormal calcifications – approach by location
 - ♦ RUQ: renal stone, adrenal calcification, gallstone, porcelain gallbladder
 - ♦ RLQ: ureteral stone, appendicolith, gallstone ileus
 - ♦ LUQ: renal stone, adrenal calcification, tail of pancreas
 - ♦ LLQ: ureteral stone
 - ♦ central: aorta/aortic aneurysm, pancreas, lymph nodes
 - ♦ pelvis: phleboliths (calcified veins), uterine fibroids, bladder stones

- **O = organs**

- kidney, liver, gallbladder, spleen, pancreas, urinary bladder, psoas shadow
- outlines can occasionally be identified because they are surrounded by more lucent fat, but all are best visualized with other imaging modalities (CT, MRI)

Approach to Abdominal Computed Tomography (CT)

- look through all images in gestalt fashion to identify any obvious abnormalities
- look at each organ/structure individually, from top to bottom evaluating size and shape of each area of increased or decreased density
- evaluate the following
 - soft tissue window
 - ♦ liver, gallbladder, spleen and pancreas
 - ♦ adrenals, kidneys, ureters and bladder
 - ♦ stomach, duodenum, small bowel mesentery and colon/appendix
 - ♦ retroperitoneum: aorta, vena cava and mesenteric vessels; look for adenopathy in vicinity of vessels
 - ♦ peritoneal cavity for fluid or masses
 - ♦ abdominal wall and adjacent soft tissue
 - lung window
 - ♦ visible lung (bases)
 - bone window
 - ♦ vertebrae, spinal cord, and bony pelvis



Ileocecal Valve (ICV) Function in Large Bowel Obstruction

Competent ICV

Distention of large bowel between obstruction and ICV; small bowel unaffected

Higher risk of perforation, especially with cecal distention > 10 cm

Incompetent ICV

Distention of large and small bowel

CT and Bowel Obstruction

- cause of bowel obstruction rarely found on plain films – CT is best choice for imaging

CT Colonography (virtual colonoscopy)

- emerging imaging technique for evaluation of intraluminal colonic masses (i.e. polyps, tumours)
- CT scan of the abdomen after the instillation of air into a prepped colon
- computer rendering of 2D CT images into a 3D intraluminal view of the colon in order to look for masses
- lesions seen on 3D rendering masses correlated with 2D axial images
- indications: surveillance in low-risk patients, incomplete colonoscopy, staging of identified colonic lesions

Contrast Studies

Table 10. Types of Contrast Studies

Study	Description	Indications	Assessment	Diseases
Cine Esophagogram	Contrast agent swallowed Recorded for later playback and analysis	Dysphagia, swallowing incoordination, recurrent aspiration, post-op cleft palate surgery	Cervical esophagus	Aspiration, webs, Zenker's diverticulum, cricopharyngeal bar, laryngeal tumour
Barium Swallow	Contrast agent swallowed under fluoroscopy, selective images captured	Dysphagia, r/o GERD, post esophageal surgery	Thoracic esophagus	Achalasia, hiatus hernia, esophagitis, cancer, esophageal tear
Upper GI Series	Double contrast study 1) Barium to coat mucosa, then 2) Gas pills for distention Patient NPO after midnight	Dyspepsia, investigate possible UGI bleed, weight loss/anemia, post gastric surgery	Thoracic esophagus, stomach, duodenum	Ulcers, neoplasms, filling defects
Barium Enema	Colon filled retrograde with barium and air or CO ₂ Bowel prep the night before procedure	Altered bowel habits, suspected LGI bleed, weight loss, anemia, r/o large bowel obstruction, suspected perforation, check surgical anastomosis, history of polyps	Large bowel Rectum may be obscured by tube – therefore must do sigmoidoscopy to exclude rectal lesions	Diverticulosis, neoplasms, IBD, intussusception (can be reduced with barium or air enema), volvulus
Hypaque® Enema	Water soluble contrast with or without bowel prep	Post operatively to assess anastomoses for leak/obstruction, perforation	Large bowel	Perforation, obstruction
Small Bowel Follow Through	Single contrast images following UGI series	GI bleed with nondiagnostic upper GI series/barium enema, weight loss/anemia, diarrhea, IBD, malabsorption, abdominal pain, post small bowel surgery	Entire small bowel	Neoplasms, IBD, malabsorption, infection
Small Bowel Enema (enteroclysis)	Duodenal intubation 1) Barium/methyl cellulose infusion and fluoroscopic evaluation 2) CT enteroclysis with water infusion	IBD, malabsorption, weight loss/anemia, Meckel's diverticulum	Entire small bowel	Neoplasms, IBD, malabsorption, infection



Normal liver appears more dense than spleen on CT. If less dense, suspect fatty infiltration.



Liver Mass DDx
5 Hs
HCC
 Hydatid cyst
 Hemangioma
 Hepatic adenoma
 Hyperplasia (focal nodular)

Revised Estimates of Diagnostic Test Sensitivity and Specificity in Suspected Biliary Tract Disease

Archives of Internal Medicine 1998; 154(22):2573-81.

Purpose: To assess the sensitivity and specificity of tests used to diagnose cholelithiasis and acute cholecystitis, including ultrasonography, oral cholecystography, radionuclide scanning with Technetium, MRI, CT.

Study Characteristics: Meta-analysis of 30 studies evaluating the use of different imaging modalities in the diagnosis of biliary tract disease.

Participants: No limits.

Main Outcomes: Sensitivity and specificity of the different imaging modalities, using the gold standard of surgery, autopsy, or 3 month clinical follow-up for cholelithiasis. For acute cholecystitis, pathologic findings, confirmation of an alternate disease, or clinical resolution during hospitalization for cholecystitis were used as the standard.

Results: For evaluating cholelithiasis, U/S had the best unadjusted sensitivity (0.97; 95% CI, 0.95 to 0.99) and specificity (0.95, 95% CI, 0.88 to 1.00) and adjusted (for verification bias) sensitivity (0.84; 95% CI, 0.76 to 0.92) and specificity (0.99; 95% CI, 0.97 to 1.00). For evaluating acute cholecystitis, radionuclide scanning has the best sensitivity (0.97; 95% CI, 0.96 to 0.98) and specificity (0.90; 95% CI, 0.86 to 0.95).

Conclusions: U/S is the test of choice for diagnosing cholelithiasis and radionuclide scanning is the superior test for diagnosing acute cholecystitis.

Computed Tomography and Ultrasonography to Detect Acute Appendicitis in Adults and Adolescents

Annals of Internal Medicine 2004; 141(7):537-546

Purpose: To review the diagnostic accuracy of CT and ultrasonography in the diagnosis of acute appendicitis.

Study Characteristics: Meta-analysis of 22 prospective studies evaluating the use of CT or ultrasonography, followed by surgical or clinical follow-up in patients with suspected appendicitis.

Participants: Age 14 and older with a clinical suspicion of appendicitis.

Main Outcomes: Sensitivity and specificity using surgery or clinical follow-up as the gold standard. Results: CT (12 studies) had an overall sensitivity of 0.94 (95% CI, 0.91 to 0.95) and a specificity of 0.95 (95% CI, 0.93 to 0.96). Ultrasonography (14 studies) had an overall sensitivity of 0.86 (95% CI, 0.83 to 0.88) and a specificity of 0.81 (95% CI, 0.78 to 0.84).

Conclusions: CT is more accurate for diagnosing appendicitis in adults and adolescents, although verification bias and inappropriate blinding of reference standards were noted in the included studies.

Specific Visceral Organ Imaging

Liver

- U/S: assessment of cysts, abscesses, tumours, biliary tree
- CT or MRI \pm IV contrast: differentiation of benign hemangiomas from primary liver tumours [hepatocellular carcinoma (HCC)] and metastases, cirrhosis, portal hypertension
- findings
 - altered liver size, contour, density
 - fatty infiltration: decreased liver density
 - advanced cirrhosis: liver small and irregular (fibrous scarring, segmental atrophy, regenerating nodules)
 - varices (caput medusa, esophageal varices, porto-systemic shunts, dilated splenic vein)
 - splenomegaly and ascites
- investigation of liver masses
 - require contrast to visualize certain hepatic masses
 - 3 phases of enhancement following IV contrast bolus
 - ♦ arterial phase (20-30 sec)
 - early and late arterial phase possible on multidetector CT
 - late arterial phase best for discriminating hypervascular HCC
 - ♦ portal venous phase (60-70 sec)
 - provides maximum enhancement of hepatic tissue
 - most tumours supplied by hepatic artery and relatively hypovascular, therefore, appear as low-attenuation masses in portal venous phase
 - ♦ equilibrium phase (120-180 sec)

Table 11. Imaging of Liver Masses

Mass	U/S	CT
Metastases	Multiple masses of variable echotexture	Usually low attenuation on contrast enhanced scan
HCC	Single/multiple masses, or diffuse infiltration	Small: hypervascular enhances in arterial phase Large: low-attenuation
Simple Cyst	Well-defined, anechoic, acoustic enhancement	Well-defined, low attenuation, homogenous
Abscess	Poorly defined, irregular margin, hypoechoic contents	Low-attenuation lesion with an irregular enhancing wall
Hydatid Cyst	Simple/multiloculated cyst	Low-attenuation simple or multiloculated cyst; calcification
Hemangioma	Homogenous hyperechoic mass	Peripheral globular enhancement in arterial phase scans; central-filling and persistent enhancement on delayed scans
Focal Nodular Hyperplasia	Well-defined mass, central scar seen in 50%	Equal attenuation to liver in portal venous phase, enhancement in arterial phase
Hepatic Adenoma	Most common in young women taking oral contraceptives. Well-defined mass with hyperechoic areas due to hemorrhage	Well-defined margin with heterogeneous texture due to hemorrhage or fat

Spleen

- U/S, CT, and/or nuclear medicine scan
- primary lymphoma > splenic metastases
- CT for splenic trauma (hemorrhage)

Biliary Tree

- U/S
 - bile ducts usually visualized only if dilated, secondary to obstruction (e.g. choledocholithiasis, benign stricture, mass)
- CT
 - dilated intrahepatic ductules seen as branching, tubular structures following pathway of portal venous system
- ERCP, MRCP, PTC: further evaluation of obstruction and possible intervention

Pancreas

- tumours
 - U/S: mass is more echogenic than normal pancreatic tissue
 - CT: preferred modality for diagnosis/staging
- ductal dilation secondary to stone/tumour
 - MRCP: imaging of ductal system using MRI cholangiography
 - ERCP: assessment of pancreatic and bile ducts via Ampulla of Vater; therapeutic potential (stent placement, stone retrieval); complication of acute pancreatitis occurs in 5% of diagnostic procedures and 10% of therapeutic procedures
- pancreatitis and/or its complications: pseudocyst, abscess, necrosis, splenic artery aneurysm (see "itis" Imaging, DM15)

"itis" Imaging



Acute Cholecystitis

- U/S very accurate – thick wall, pericholecystic fluid, gallstones, dilated gallbladder, positive sonographic Murphy's sign
- nuclear medicine (HIDA scan) may be helpful in equivocal cases, but is not often used
 - equivalent sensitivity and specificity to ultrasound

Acute Appendicitis

- U/S very useful – thick-walled appendix, appendicolith, dilated fluid-filled appendix, non-compressible
- U/S may also demonstrate other causes of RLQ pain (e.g. ovarian abscess, IBD, ectopic pregnancy)
- CT: enlargement of appendix (>6 mm in outer diameter), enhancement of appendiceal wall, adjacent inflammatory stranding, appendicolith; also facilitates percutaneous abscess drainage

Acute Diverticulitis

- most common site is rectosigmoid (diverticula are outpouchings of colon wall)
- CT is imaging modality of choice, although U/S is sometimes used
 - oral and rectal contrast given before CT to opacify bowel
 - cardinal signs: thickened wall, mesenteric infiltration, gas-filled diverticula, abscess
 - CT can be used for percutaneous abscess drainage before or in lieu of surgical intervention
 - sometimes difficult to distinguish from perforated cancer (therefore send abscess fluid for cytology and follow up with colonoscopy)
 - if chronic, may see fistula (most common to bladder) or sinus tract (linear or branching structures)

Acute Pancreatitis

- clinical/biochemical diagnosis
- imaging used to support diagnosis and evaluate for complications (diagnosis cannot be excluded by imaging alone)
- U/S good for screening and follow-up of a hypoechoic enlarged pancreas (although useless if ileus present as gas obscures pancreas)
- CT is useful in advanced stages of pancreatitis and in assessing for complications and is increasingly becoming the 1st line imaging test
 - enlarged pancreas, edema, stranding changes in surrounding fat with indistinct fat planes, mesenteric and Gerota's fascia thickening, pseudocyst in lesser sac, abscess (gas or thick-walled fluid collection), pancreatic necrosis (low attenuation gas-containing non-enhancing pancreatic tissue), hemorrhage
 - CT-guided needle aspiration and/or drainage done for abscess when clinically indicated
 - pseudocyst may be followed by CT and drained if symptomatic

Angiography of GI Tract

- GI tract arterial blood supply
 - celiac artery: hepatic, splenic, gastroduodenal, left/right gastric
 - superior mesenteric artery (SMA): jejunal, ileal, ileo-colic, right colic, middle colic
 - inferior mesenteric artery (IMA): left colic, superior rectal
- imaging of GI tract vessels
 - conventional angiogram: invasive (usual approach via femoral puncture), catheter used
 - ♦ flush aortography: catheter injection into abdominal aorta, followed by selective arteriography of individual vessels
 - CT angiogram: non-invasive using IV contrast (no catheterization required)

Genitourinary System

Modalities

KUB (kidneys, ureters, bladder)

- a frontal supine radiograph of the abdomen
- useful in evaluation of radio-opaque renal stones (all stones but uric acid and indinavir), as well as indwelling ureteric stents or catheters
- addition of intravenous contrast excreted by the kidney (intravenous urogram) allows greater visualization of the urinary tract, but has been largely replaced by CT urography



Imaging Modality Based on Presentation

- Acute testicular pain = Doppler, U/S
- Amenorrhea = U/S, MRI (brain)
- Bloating = U/S, CT
- Flank pain = U/S, CT
- Hematuria = U/S, Cystoscopy, CT
- Infertility = Hysterosalpingogram, MRI
- Lower abdominal mass = U/S, CT
- Lower abdominal pain = U/S, CT
- Renal colic = U/S, KUB, CT
- Testicular mass = U/S
- Urethral stricture = Urethrogram

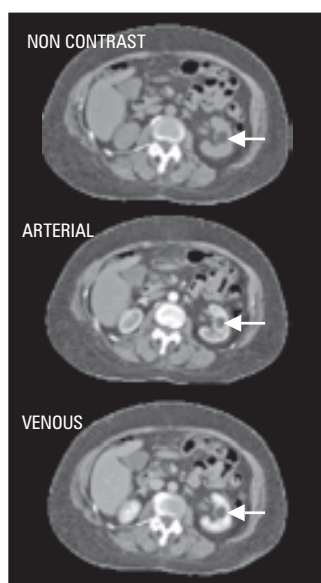


Figure 8. Triphasic CT of an Angiomyolipoma – showing fat density with non-contrast scan, mildly enhancing with contrast

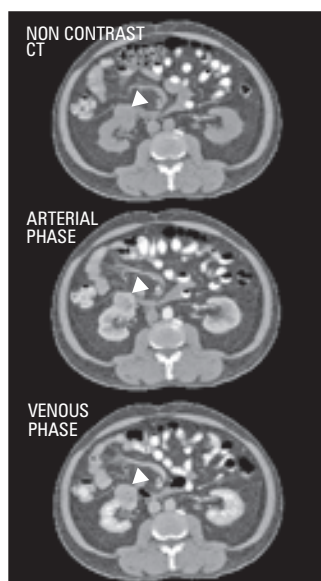


Figure 9. Triphasic CT of a Renal Cell Carcinoma – showing arterial enhancement and venous de-enhancement



Figure 10. Retrograde Urethrogram – demonstrating stricture in the membranous urethra

Abdominal CT

• plain CT

- good for general imaging of renal anatomy, although specific study types have supplanted plain CT for many indications, including CT urography (upper tract uroepithelial malignancies and renal calculi) and triphasic CT (renal masses)

• CT urography

- excretory phase imaging allows detailed assessment of urinary tracts
- high sensitivity (95%) for uroepithelial malignancies of the upper urinary tracts
- also useful for assessment of renal calculi

• triphasic CT

- standard imaging for renal masses
- comprised of unenhanced, nephrographic, and excretory phases
- allows accurate assessment of renal arteries and veins and better characterization of suspicious renal masses, with particular utility in differentiating renal cell carcinoma from more benign masses

U/S

- initial study for evaluation of kidney size and nature of renal masses (solid vs. cystic renal masses vs. complicated cysts)
- technique of choice for screening patients with suspected hydronephrosis (no intravenous contrast injection, no radiation to patient, and can be used in patients in renal failure)
- solid renal masses: echogenic (bright on U/S)
- cystic renal masses: smooth well-defined walls with anechoic interior (dark on U/S)
- complicated cysts: internal echoes within a thickened, irregular-walled cyst
- transrectal U/S (TRUS) useful to evaluate prostate gland and guide biopsies
- Doppler U/S to assess renal vasculature

Retrograde Pyelography

- used to visualize the urinary collecting system via a cystoscope, ureteral catheterization, and retrograde injection of contrast medium
- ordered when the intrarenal collecting system and ureters cannot be opacified using intravenous techniques (patient with impaired renal function, high grade obstruction)
- only yields information about the collecting systems (renal pelvis and associated structures)
 - no information regarding the parenchyma of the kidney

Voiding Cystourethrogram (VCUG)

- bladder filled with contrast to the point where voiding is triggered
- real-time images via fluoroscopy (continuous x-ray imaging) to visualize bladder
- contractility and evidence of vesicoureteric reflux
- indications: children with recurrent UTIs, hydronephrosis, hydroureter, suspected lower urinary tract obstruction or vesicoureteral reflux

Retrograde Urethrogram

- used mainly to study strictures or trauma to the male urethra (Figure 10)

MRI

- strengths: high spatial and tissue resolution, lack of exposure to ionizing radiation and nephrotoxic contrast agents
- indicated over CT for depiction of renal masses in patients with previous nephron sparing surgery, patients requiring serial follow-ups (less radiation dosage), patients with reduced renal function, and patients with solitary kidneys

Renal Scan

- 2 radionuclide tests for kidney – renogram and morphological scan
- renogram
 - to assess renal function and collecting system
 - useful in evaluation of renal failure, workup of urinary tract obstruction and hypertension, investigation of renal transplant
 - intravenous injection of a radionuclide, technetium-99m pentetate (Tc99m-DTPA) or iodine-labeled hippurate, and imaged at 1-second intervals with a gamma camera over 30 minutes to assess perfusion
 - ♦ delayed static images over the next 30 minutes can be used to assess renal function and the collecting system
- morphological
 - to assess renal anatomy
 - study done with Tc99m-DMSA and Tc99m-glucoheptonate
 - useful in investigation of renal mass and cortical scars

Gynecological Imaging

U/S

- transabdominal and transvaginal are the primary modalities, and are indicated for different scenarios
- transabdominal requires a full bladder to push out air containing loops of bowel
 - good initial investigation for suspected pelvic pathology
- transvaginal approach provides enhanced detail of deeper/smaller structures by allowing use of higher frequency sound waves at reduced distances
 - improved assessment of ovaries, first trimester development, and ectopic pregnancies

Hysterosalpingogram

- useful for assessing pathology of the uterine cavity and fallopian tubes, performed by x-ray images of the pelvis after cannulation of the cervix and subsequent injection of opacifying agent
- particularly useful for evaluating uterine abnormalities (bicornuate uterus), or evaluation of fertility (absence of flow from tubes to peritoneal cavity indicates obstruction)

CT/MRI

- excellent for evaluating pelvic structures, especially those adjacent to the adnexa and uterus
- invaluable for staging gynecological malignancies

Selected Pathology

Renal Masses

- Bozniak classification for cystic renal masses
 - classes I-II are benign and can be disregarded
 - class IIF should be followed
 - classes III-IV are suspicious for malignancy, requiring additional workup

Table 12. Bozniak Classification for Cystic Renal Masses

Classes	Definition
Simple renal cysts	
Class I	Fluid-attenuating well-defined lesion, no septation, no calcification, no solid components, hair thin wall
Class II	Same as class I + fine calcification or moderately thickened calcification in septae or walls; also includes hyperdense cysts (<3 cm) that do not enhance with contrast
Complex renal cysts	
Class III	Thick irregular walls, \pm calcifications, \pm septated, enhancing walls or septa with contrast
Renal cell carcinoma	
Class IV	Same as class III + soft tissue enhancement with contrast (defined as >10 Hounsfield unit increase, characterizing vascularity) with de-enhancement in venous phase \pm areas of necrosis

- angiomyolipoma (a benign renal neoplasm composed of fat, vascular, and smooth muscle elements)
 - fat density seen on non-contrast CT (<-10 Hounsfield units), some enhancement with contrast (less than renal cell carcinoma)

Neuroradiology

Modalities

- CT is modality of choice for most neuropathology; even under circumstances when MRI is preferred, CT is frequently the initial study because of its speed, availability and lower cost
- CT is preferred for
 - acute head trauma: CT is best for visualizing "bone and blood"; MRI is used in this setting only when CT fails to detect an abnormality in the presence of strong clinical suspicion
 - acute stroke (MR ideal, CT most frequently used)
 - suspected subarachnoid or intracranial hemorrhage
 - meningitis: rule out mass effect (e.g. cerebral herniation, shift) prior to lumbar puncture
 - tinnitus and vertigo: CT and MRI are used in combination to detect bony abnormalities and CN VIII tumours, respectively

Skull Films

- rarely performed; CT is modality of choice
- indications include
 - screening for destructive bony lesions (e.g. metastases)
 - metabolic disease
 - skull anomalies
 - post-operative changes/post-operative confirmation of hardware placement
 - skeletal surveys
- generally not indicated for non-penetrating head trauma



Figure 11. Transabdominal Ultrasound – pregnancy, 18 wk fetus



Figure 12. Hysterosalpingogram – showing left hydrosalpinx



Pregnancy should always be ruled out by beta-HCG before CT of a female pelvis (or any organ system) is performed.



Attenuation
Bone (= bright) > grey matter > White matter ("fatty" myelin) > CSF > air (= dark)



Modality Based on Presentation

- Cognitive decline = CT
- Cord compression = MRI
- Decreased LOC = CT
- Fish bone = CT
- LBP, radiculopathy = MRI
- Multiple sclerosis = MRI
- Neck infection = CT
- Orbital infection = CT
- R/O bleed = CT
- R/O aneurysm = CTA, MRA
- Seizure = CT
- Sinusitis = CT
- Stroke = CT, MRI
- Trauma = CT
- Weakness, systemically unwell = CT



DDx for Ring Enhancing Lesion on CT with Contrast

MAGICAL DR

*Metastases
*Abscess
*Glioblastoma (high grade astrocytoma)
Infarct
Contusion
AIDS
Lymphoma
Demyelination
Resolving hematoma

[* by far the 3 most common Dx's]

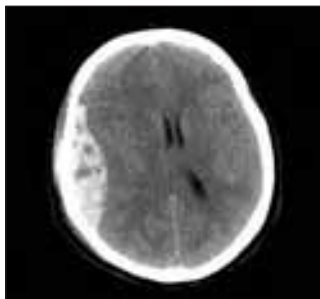


Figure 13. Epidural Hematoma

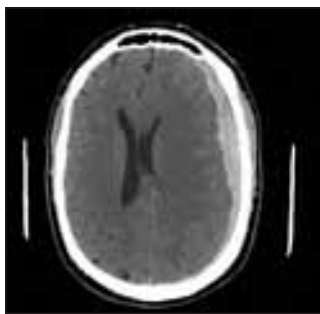


Figure 14. Subdural Hematoma

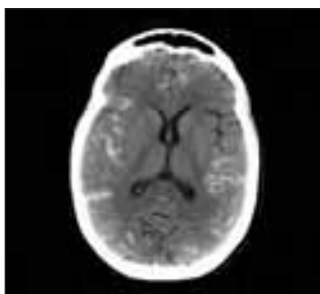


Figure 15. Subarachnoid Hematoma

CT

- excellent study for evaluation of bony abnormalities
- often done first without and then with intravenous contrast to show vascular structures or anomalies
- vascular structures and areas of blood-brain barrier impairment are opaque (e.g. hyperattenuating or white/show enhancement) with contrast injection
 - when in doubt, look for circle of Willis or confluence of sinuses to determine presence of contrast enhancement
- posterior fossa can be obscured by extensive bony artifact
- rule out skull fracture, epidural hematoma (lenticular shape), subdural hematoma (crescentic shape), subarachnoid hemorrhage, space occupying lesion, hydrocephalus, and cerebral edema
- multiplanar imaging can be performed with newer generation of CT scanners

Myelography

- introduction of water-soluble, low-osmotic-contrast media into subarachnoid space using lumbar puncture followed by x-ray or CT scan
- excellent study for disc herniations, traumatic nerve root avulsions
- use has decreased due to MRI

MRI (see Table 1)

- shows brain and spinal soft tissue anatomy in fine detail
- clearly distinguishes white from grey matter (especially T1-weighted series)
- multiplanar reconstruction helpful in pre-op assessment

Cerebral Angiography/CT Angiography/MR Angiography

- evaluation of vascular lesions such as atherosclerotic disease, aneurysms, vascular malformations, arterial dissection
- conventional digital subtraction angiography (DSA) remains the gold standard for the assessment of neck and intracranial vessels; however, it is an invasive procedure requiring arterial (femoral) puncture; catheter manipulation has risk of vessel injury (e.g. dissection, occlusion, vasospasm)
- MR angiography (MRA) methods (phase contrast, time of flight, gadolinium-enhanced) and CT angiography (CTA) are much less invasive without actual risk to intracranial or neck vessels
- MRA and CTA are often used first as 'screening tests' for the assessment of subarachnoid hemorrhage, vasospasm, aneurysms

Nuclear Medicine

- SPECT using HMPAO (technetium-99m labelled derivative of propylamine oxane) imaging assesses cerebral blood flow by diffusing rapidly across the blood brain barrier and becoming trapped within cells
- PET imaging assesses cerebral metabolic activity

Approach to CT Head

- think anatomically, work from superficial to deep
- **scan** – confirm that the imaging is of the patient of interest, whether contrast was used, if the patient is aligned properly, if there is artifact present
- **skin/soft tissue** – examine the soft-tissue superficial to the skull, looking for thickening suggestive of hematoma or edema; also investigate: ear, orbital contents (globe, fat, muscles), parotid, muscles of mastication (masseter, temporalis, pterygoids), visualized pharynx
- **bone and airspace** (use the bone window) – check calvarium, visualized mandible, visualized c-spine (usually C1 and maybe part of C2) for fractures, absent bone, lytic/sclerotic lesions; inspect sinuses and mastoid air cells for opacity that may suggest fluid, pus, blood, tumour, or fracture
- **dura and subdural space** – look for crescent-shaped hyperdensity in the subdural space as evidence of subdural hematoma; look for a lentiform hyperdensity in epidural space as evidence of epidural hematoma; check symmetry of dural thickness, where increased thickness may suggest the presence of blood
- **parenchyma** – look for symmetry of the parenchyma for evidence of midline shift; look for poor contrast between grey and white matter as evidence of possible infarction, tumour, edema, infection, or contusion; look for hyperdensities in the parenchyma suggestive of enhancing lesions, intracerebral hemorrhage, or calcification; central grey matter nuclei should be visible, including globus pallidus, putamen, and internal capsule, otherwise suspect infarct, tumour, or infection
- **ventricles/sulci/cisterns** – examine position of ventricles for evidence of midline compression/shift; look for hyperdensities in the ventricles indicative of ventricular/subdural hemorrhage; look at ventricular size for evidence of hydrocephalus; obliteration of sulci may suggest presence of edema causing effacement, possible blood filling in the sulci, or tumour; cistern hyperdensities may suggest blood, pus, or tumour



Approach to the CT Head

Some = Scan
Sore = Skin/Soft Tissue
Brains = Bone/Airspace
Demonstrate = Dura/Subdural space
Pushed = Parenchyma
Ventricles = Ventricles/Sulci/Cisterns



Transient ischemic attacks are not associated with radiological findings.



DDx Suspected MS lesion

Vasculopathy: ischemia, vasculitis, hypertension, migraine
Demyelinating disease: progressive multifocal leukoencephalopathy, age-related
Inflammatory process: sarcoid, lyme, primary/metastatic cancer

Selected Pathology

- see Neurosurgery, NS4-23 for intracranial mass lesions
- see Neurosurgery, NS29-36 and Plastic Surgery, PL26 for head trauma
- see Emergency Medicine, ER7 for vertebral trauma
- see Neurosurgery, NS22-29 and Orthopaedics, OR22 for degenerative spinal abnormalities

CEREBROVASCULAR DISEASE (see Neurology, N44-48 and Neurosurgery, NS17-22)

- carotid artery disease
 - evaluate with Duplex Doppler U/S
 - MR angiography or CT angiography if carotid angioplasty or endarterectomy is under consideration (conventional angiography reserved for inadequate MRA or CTA)
- infarction
 - early changes
 - ♦ CT
 - usually normal within 6 hours of infarction
 - edema (loss of grey-white matter differentiation – “insular ribbon” sign, effacement of sulci, mass effect)
 - within 24 hours, development of low-density, wedge-shaped area of infarction extending to periphery (correlating to vascular territory distal to affected artery)
 - refer to **Functional Neuroanatomy software** (online)
 - in case of ischemic stroke, may see hyperattenuating (bright) artery (hyperdense MCA sign) represents intravascular thrombus or embolus
 - in case of hemorrhagic stroke or transformation (common in basal ganglia and cortex), may see bright acute blood surrounded by edema
 - ♦ MRI
 - edema with high signal on T2-weighted images and FLAIR (fluid-attenuated inversion-recovery) image (loss of grey-white matter differentiation, effacement of sulci, mass effect)
 - diffusion-weighted image (DWI) shows acute high signal changes demonstrating restricted movement of water (indicative of cytotoxic edema)
 - apparent diffusion coefficient (ADC) image shows low signal intensity in acute ischemia (nadir 3-5 days, returns to baseline 1-4 weeks)
 - subacute changes (CT and MRI)
 - ♦ edema and mass effect more prominent
 - ♦ gyral enhancement with contrast indicative of blood-brain barrier breakdown
 - chronic changes (CT and MRI)
 - ♦ encephalomalacia (parenchymal volume loss) with dilatation of adjacent ventricles

Multiple Sclerosis (MS)

- acute phase: plaques undergo inflammatory reaction with edema, cellular infiltration, and spectrum of demyelination
- chronic phase: astrocytic hypoplasia, resolution of cellular inflammation, and loss of myelin
- MRI is the most sensitive diagnostic test (>90%), but not specific
 - ischemic demyelination can produce similar features
 - confluent multiple sclerosis lesions can be mistaken for a neoplasm
 - specificity greatly improved if periventricular plaques are accompanied by lesions in the cerebellum, cerebral peduncles, corpus callosum, and spinal cord
- T2-weighted MRI shows multiple hyperintense round or ovoid white matter plaques from myelin breakdown in periventricular or subcortical distribution
- “Dawson’s fingers” are seen as radiating, elongated areas of T2 signal extending from the ventricles; these represent demyelination along medullary veins (Figure 18)
- T1-weighted MRI shows iso- or low intensity regions (“black-holes”)
- most common locations include periventricular white matter (>80%), corpus callosum (particularly at callosal-septal interface, 50-80%), visual pathways (optic neuritis), posterior fossa, and brainstem
- FLAIR imaging superior for supratentorial white matter lesions; may not detect posterior fossa, brainstem, and spinal lesions
- enhancement lasts 2-8 weeks but may persist for 6+ months; clinical suspicion for neoplasm required if nodule/plaque enhances for 3+ months
- lesions tend to be confluent and >6 mm in diameter
- new lesions with active demyelination may enhance with gadolinium contrast, ranging from nodular enhancement to ring or arc shaped; older, less active lesions do not enhance



Early Signs of Brain Infarction at CT: Observer Reliability and Outcome after Thrombolytic Treatment – Systematic Review

Radiology 2005; 235:444-453

Study: Systematic review of 15 studies between 1990-2003 that investigated inter-observer agreement of early CT signs of acute ischemic stroke, and prognostic value of early CT signs in patient outcome. There was a median of 30 CTs and 6 raters per study.

Patients: 3468 adult patients who underwent CT within 6 hours of stroke.

Main Outcome: Degree of inter-observer agreement between stroke signs on CT, and risk of death or dependency (using validated stroke scales) based on CT signs using after 1-3 months.

Results: Prevalence of all early infarction signs was $61\% \pm 21$, and interobserver agreement was 0.14-0.78 (K statistic) for any early infarct sign. Average sensitivity of detecting early ischemic stroke was 66% (range 20%-87%) and average specificity was 87% (range 56%-100%). Experience improved detection, but knowledge of patient history did not. An increased risk of poor outcome (death or dependency) was associated with any early infarction sign, with an odds ratio of 3.11 (95%CI, 2.77-3.49).

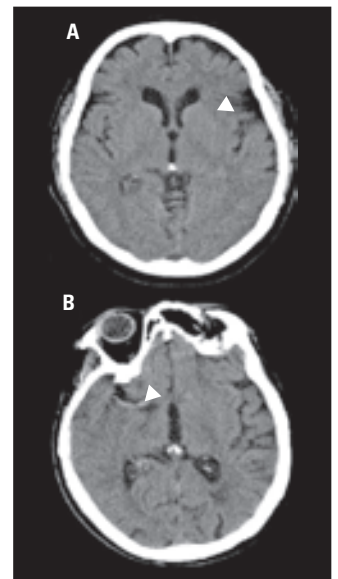


Figure 16. CT Images of Early Infarct – showing (A) absence of left insular ribbon (B) hyperdense artery



Figure 17. Diffusion Weighted Imaging of Patient with Normal CT – demonstrates right frontotemporal infarct

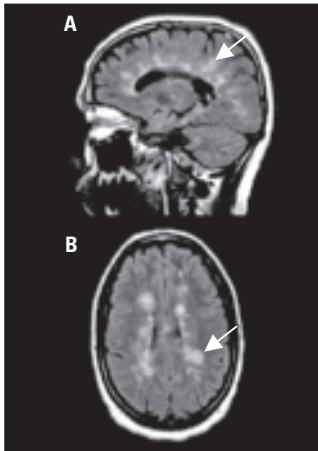


Figure 18. T2-weighted FLAIR
– (A) sagittal (B) axial images of multiple sclerosis with periventricular “Dawson’s Fingers”



Figure 19. T2-weighted (FLAIR)
Coronal Image of HSV Encephalitis
Affecting Temporal Lobes

CNS Infections

• leptomeningitis

- inflammation of the pia or arachnoid mater, most often secondary to hematogenous spread from infection or via organisms gaining access across areas not protected by the blood brain barrier (choroid plexus or circumventricular organs)
- pathogens include: *S. pneumoniae*, *H. influenza*, *N. meningitidis*, *L. monocytogenes*
- best visualized with MRI (T2-weighted/FLAIR) over CT
- findings include
 - ♦ meningeal enhancement (following the gyri/sulci, and/or basal cisterns), hydrocephalus (communicating), cerebral swelling, subdural effusion
 - ♦ a normal MRI does not rule out leptomeningitis

• herpes simplex encephalitis (see [Infectious Diseases](#), ID6)

- inflammation of the brain parenchyma secondary to HSV infection
- asymmetrically affects the temporal lobes, orbitofrontal region, insula, and cingulate gyrus
- best imaged with MRI (T1- and T2-weighted imaging)
- findings include
 - ♦ acute (within 4-5 days): high intensity lesions on T2 MRI in temporal and inferior frontal lobes, asymmetric
 - strongly suggestive of HSV encephalitis
 - DDx: infarct, tumour, status epilepticus, limbic encephalitis
 - ♦ CT may show low density in temporal lobe and insula; rarely basal ganglia involvement
 - ♦ long term may show parenchymal loss to affected areas

• cerebritis/cerebral abscess

- an infection of the brain parenchyma (cerebritis) which can progress to a collection of pus (abscess), most frequently due to hematogenous spread of infectious organisms
- commonly located in the distribution of the middle cerebral artery
- pathogens include: *S. aureus* (often in IVDU, nosocomial), GN bacteria, *Streptococcus*, *Bacteroides*
- findings according to one of four stages of abscess formation:
 - ♦ early cerebritis (1-3 days) – inflammatory infiltrate with necrotic centre, low intensity on T1, high intensity on T2
 - ♦ late cerebritis (4-9 days) – ring enhancement may be present
 - ♦ early capsule (10-13 days) – ring enhancement
 - ♦ late capsule (14 days or greater) – well demarcated ring-enhancing lesion, low intensity core, with mass effect; considerable edema around the lesion, seen as hyperdensity on T2

Musculoskeletal System (MSK)

Modalities

Plain Film/X-Ray

- usually initial study used in evaluation of bone and joint disorders
- indications: fractures and dislocations, arthritis, assessment of malalignment, assessment of orthopedic hardware, initial assessment of bone tumours
- minimum of two films orthogonal to each other (usually AP and lateral) to rule out a fracture
- image proximal and distal joints (particularly important with paired bones, e.g. radius/ulna)
- not very effective in evaluating soft tissue injury
- strengths: fast, inexpensive, readily available, reproducible

CT

- evaluation of fine bony detail
- indications: assessment of complex, comminuted, intra-articular or occult fractures including distal radius, scaphoid, skull, spine, acetabulum, calcaneus, and sacrum
- evaluation of soft tissue calcification/ossification
- strengths: fast, reproducible, excellent bone evaluation, and spatial resolution
- drawbacks: radiation dose, relatively poor soft tissue characterization in comparison with U/S and MRI

MRI

- indications: evaluation of internal derangement of joints (ligaments, joint capsule, menisci, labrum, cartilage), assessment of tendons and muscle injuries, characterization and staging of soft tissue and bony masses
- strengths: excellent soft tissue contrast, multiplanar imaging, no radiation
- drawbacks: long imaging times, expense, claustrophobia, contraindications (e.g. pacemakers, orbital metallic bodies), artifact around metal hardware



Plain Film First for Fractures
CT for Cortex
MRI for Marrow



Approach to Fractures

1. Look for soft tissue swelling
2. Look for fracture lines (abnormal black lines)
3. Look for discontinuation/disruption of cortex
4. Look for displacement and angulation
5. Look for fracture extension into the joint

See [Orthopaedics](#), OR5

Ultrasound

- indications: tendon injury (e.g. rotator cuff, Achilles tendon), detection of soft tissue masses and to determine whether cystic or solid, detection of foreign bodies, ultrasound guided biopsy and injections
- Doppler – determines vascularity of structures
- strengths: good soft tissue evaluation, easy contralateral comparison, dynamic imaging
- weaknesses: operator dependent, steep learning curve, poor for bone evaluation

Nuclear Medicine (Skeletal Scintigraphy)

- determine the location and extent of bony lesions
- radioisotopes localize to areas of increased bone turnover or calcification – growth plate in children, tumours, infections, fractures, metabolic bone disease (e.g. Paget's), sites of reactive bone formation, and periostitis
- very sensitive, not specific (trauma, infection, inflammation look similar)

Approach to Interpretation of Bone X-Rays

- identification – name, MRN, age of patient, type of study, region of investigation
- soft tissues – swelling, calcification/ossification
- joints – alignment, joint space, presence of effusion, osteophytes, erosions, bone density, overall pattern, and symmetry of affected joint
- bone – periosteum, cortex, medulla, trabeculae, density, articular surfaces, bone destruction, bone production, appearance of the edges or borders of any lesions (Figure 20)

Trauma

Fracture/Dislocation

- description of fractures
 - patient (name, MRN, age, sex)
 - views (e.g. AP and lateral of right wrist)
 - site of fracture
 - ♦ bone (e.g. tibia, scaphoid, etc.)
 - ♦ region of bone (e.g. proximal, distal, metaphyseal, epiphyseal, diaphyseal)
 - ♦ intra-articular vs. extra-articular
 - pattern of fracture line
 - ♦ simple: a single break divides bone in two pieces
 - ♦ comminuted: bone broken into more than two pieces
 - displacement (distal fragment with reference to the proximal fragment)
 - soft tissue involvement
 - ♦ calcification, gas, foreign bodies
 - ♦ open (compound) vs. closed
 - ♦ type of fracture
 - stress: fracture due to repetitive trauma
 - pathologic: fracture in area of bone weakened by disease
- for specific fracture descriptions and characteristics of fractures, see [Orthopaedics](#), OR5



Types of Fractures

- Transverse
- Oblique
- Spiral
- Avulsion
- Impacted



Types of Displacements

- Translation
- Angulation
- Rotation
- Impaction
- Dislocation

Arthritis

Radiographic Hallmarks of OA

- joint space narrowing – typically non-uniform
- subchondral sclerosis
- subchondral cyst formation
- osteophytes

Radiographic Hallmarks of RA

- soft tissue swelling
- periarticular osteopenia
- joint space loss – typically uniform
- erosions

Bone Tumour

Approach

- metastatic tumours to bone are much more common than primary bone tumours, particularly if age >40 years
 - diagnosis usually requires a biopsy if primary not located
 - few benign tumours/lesions have potential for malignant transformation
 - MRI is good for tissue delineation and preoperative assessment of surrounding soft tissues, neurovascular structures, and medullary/marrow involvement
 - plain film is less sensitive than other modalities but useful for assessing aggressiveness and constructing differential diagnosis

**Benign Lesions which may have****Aggressive Features**

- Osteomyelitis
- Osteoblastoma
- Aneurysmal bone cyst
- Langerhans cell histiocytosis
- Myositis ossificans

**Periosteal Reaction**

"Onion skinning": Ewing's sarcoma
 "Sunburst", "hair on end": osteosarcoma
 "Codman's triangle": osteosarcoma, Ewing's sarcoma, subperiosteal abscess



Lytic = decreased density
 Sclerotic = increased density

Considerations and Tumour Characteristics

- age – most common tumours by age group
 - <1 year of age: metastatic neuroblastoma
 - 1-20 years of age: Ewing's tumour in tubular bones
 - 10-30 years of age: osteosarcoma and Ewing's tumour in flat bones
 - >40 years of age: metastases, multiple myeloma, and chondrosarcoma
- multiplicity: metastases, myeloma, lymphoma, fibrous dysplasia, enchondromatosis
- location within bone
 - epiphysis: giant cell tumour, chondroblastoma, geode, eosinophilic granuloma, infection
 - metaphysis: simple bone cyst, aneurysmal bone cyst, enchondroma, chondromyxoid fibroma, nonossifying fibroma, osteosarcoma, chondrosarcoma
 - diaphysis: fibrous dysplasia, aneurysmal bone cysts, brown tumours, eosinophilic granuloma, Ewing's sarcoma
- margins/zones of transition
 - transition area from normal bone to area of lesion reflects aggressiveness of the lesion
 - well-defined lesion with narrow zone of transition (i.e. sharp cut-off between normal and abnormal) suggests a non-aggressive process
 - thin sclerotic margin is also suggestive of a non-aggressive process
 - an ill-defined lesion with a permeative pattern is suggestive of an aggressive lesion
- expansile
 - aneurysmal bone cyst, giant cell tumour, enchondromas, brown tumours, metastases (especially renal and thyroid), plasmacytoma
- cortex
 - intact cortex is more likely benign
 - destruction of cortex is more likely aggressive
- periosteal reaction
 - mature well-formed solid periosteal reaction: most likely a non-aggressive process
- matrix mineralization
 - chondroid (popcorn calcification) or osseous
- soft tissue
 - soft tissue mass: seen in aggressive tumours
- see Figure 20 and Table 13

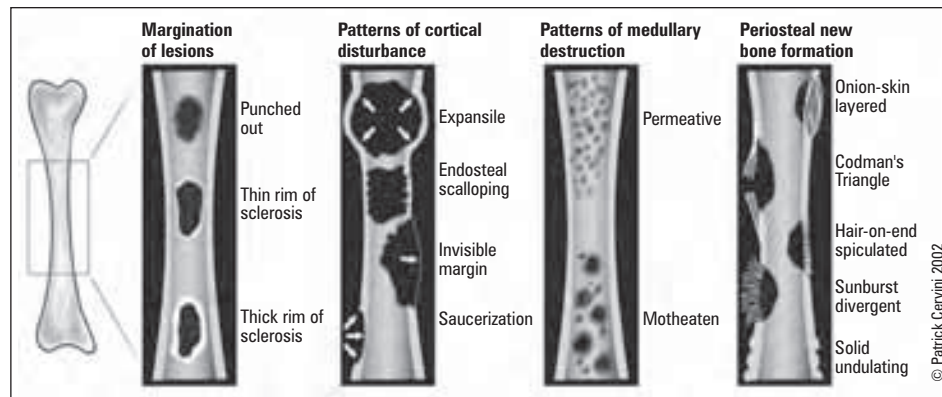


Figure 20. Radiographic Appearance of Bone Remodelling and Destruction Processes

Table 13. Characteristics of Benign and Malignant Bone Lesions

Benign	Malignant
Single lesion	Multiple lesions (metastatic/multiple myeloma) (some syndromes have multiple benign lesions)
No bone pain	Bone pain
Sharp area of delineation	Poor delineation of lesion – wide zone of transition
Overlying cortex intact	Loss of overlying cortex/bony destruction
No or simple periosteal reaction	Periosteal reaction – aggressive
Sclerotic margins with sharp zone of transition	Wide zone of transition
No soft tissue mass	Soft tissue mass

Note: for specific bone tumours see [Orthopaedics, OR42](#)

Metastatic Bone Tumours

- all malignancies have potential to metastasize to bone
- metastases are 20-30x more common than primary bone tumours
 - metastasis can cause a lytic (decreased density) or a sclerotic (increased density) reaction when seeding to bone
- when a primary malignancy is first detected, a bone scan is often part of the initial work-up
- may present with pathological fractures or pain
- biopsy or determination of primary is the only way to confirm the diagnosis
- for most common metastatic bone tumours, see [Orthopaedics](#), OR43

Table 14. Characteristic Bone Metastases of Common Cancers

Lytic	Sclerotic	Expansile	Peripheral
Breast	Prostate	Thyroid	Lung
Lung	Breast	Renal	Kidney
Thyroid	Lymphoma		Melanoma
Kidney	Lung		
Multiple myeloma	Treated tumours		

Infection

Osteomyelitis

- Tc99m, followed by indium-111 labeled white cell scan or gallium radioisotope scan is the best modality to establish the presence of bone infection
- plain film
 - visible 8-10 days after process has begun
 - osteomyelitic changes on plain film
 - ♦ soft tissue swelling that is deep and extends from the bone with loss of tissue planes (because fat becomes edematous)
 - ♦ local periosteal reaction
 - ♦ pockets of air (from anaerobes) may be seen in the tissues
 - ♦ metaphysis over the area of infection may appear mottled and nonhomogeneous with a classic “moth-eaten” appearance
 - ♦ cortical destruction

Bone Abscess

- overlying cortex has periosteal new bone formation
- sharply outlined radiolucent area with variable thickness in zone of transition
- variable thickness periosteal sclerosis
- sequestrum: a piece of dead bone within a Brodie's abscess
- a sinus tract or cloaca may communicate between the abscess through the cortex to the surface of the bone

Metabolic Bone Disease

Osteoporosis

- with increasing age, hormonal changes lead to bone resorption exceeding bone formation
- reduction in amount of normal bone; fewer and thinner trabeculae; diffuse process; affecting all bones
- dual x-ray absorptiometry (DEXA) – gold standard for measuring bone mineral density
 - T-score: the number of standard deviations from the young adult mean
 - ♦ used to diagnose osteoporosis and is a measure of current fracture risk
 - ♦ clinically most valuable
 - ♦ $-2.5 < T < -1$ = osteopenia
 - ♦ $T \leq -2.5$ = osteoporosis
 - Z-score: the number of standard deviations from the age-matched mean
 - risk of fracture: related to bone mineral density, age, history of previous fractures, steroid therapy
- appearance on plain film
 - osteopenia: reduced bone density on plain films
 - ♦ may also be seen with osteomalacia, hyperparathyroidism, and disuse
 - compression of vertebral bodies
 - biconcave vertebral bodies (“codfish” vertebrae)
 - long bones have appearance of thinned cortex and increased medullary cavity
 - look for complications of osteoporosis
 - ♦ e.g. insufficiency fractures: hip, vertebrae, sacrum, pubic rami



Diagnostic sensitivity of DEXA highest when BMD measured at lumbar spine and proximal femur.



Osteoporosis
Reduced amount of bone

OsteoMalacia
Normal amount of bone, but reduced Mineralization of normal osteoid

Osteomalacia/Rickets

- reduction in bone density due to seams of unmineralized osteoid
- initial radiological appearance of both osteoporosis and osteomalacia is osteopenia (coarse and poorly defined bone texture)
- “fuzzy”, ill-defined trabeculae
- softening and bowing of long bones
- Looser’s zones (pseudofracture)
 - characteristic radiological feature
 - fissures or clefts at right angles to long bones and extending through cortex
- DDx: osteomalacia, chronic renal disease, fibrous dysplasia, hyperthyroidism, Paget’s, osteodystrophy, X-linked hypophosphatemia

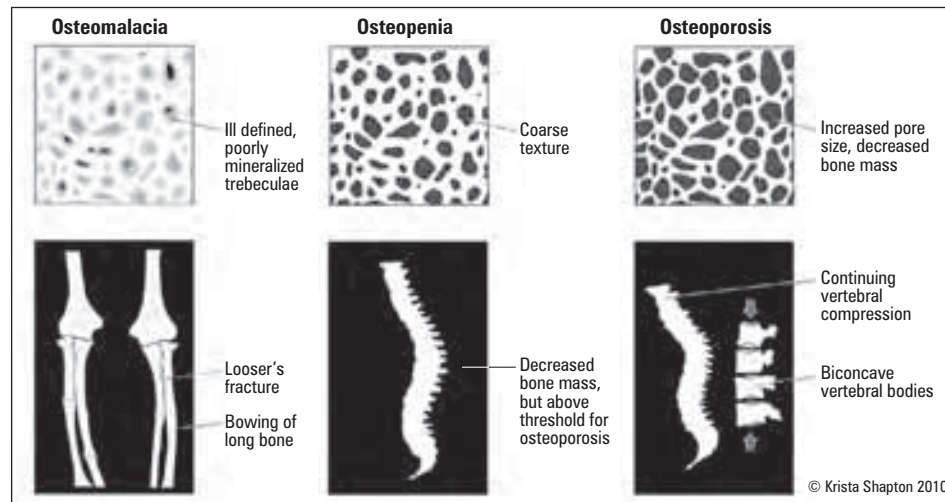


Figure 21. Osteomalacia, Osteopenia and Osteoporosis

Hyperparathyroidism

- most common cause is renal failure (secondary hyperparathyroidism)
- skeletal manifestations of chronic renal insufficiency
- chondrocalcinosis
 - calcifications of the soft tissues (including arteries and peri-articular soft tissue)
 - resorption of bone typically in hands (subperiosteal and at tufts), SI joints (subchondral), skull (“salt and pepper” appearance), osteoclastoma (brown tumours)
 - “rugger jersey spine”: band-like osteosclerosis at superior/inferior margins of vertebral bodies
- see [Endocrinology](#), E39

Paget’s Disease

- abnormal remodeling of bone – especially skull, spine, pelvis
- may involve single or multiple bones
- 3 phases: 1st lytic, 2nd mixed (lytic/sclerotic), 3rd sclerotic
- features
 - coarsening of the trabeculae with bone expansion
 - bone softening/bowing
 - bone scan will reveal high activity, especially at bone ends
 - thickened cortex
- complications
 - pathological fractures
 - cardiac failure
 - early OA
 - nerve entrapment in base of skull
 - malignant degeneration

Nuclear Medicine



Thyroid

Radioactive Iodine Uptake (see [Endocrinology](#), E20)

- index of thyroid function (trapping and organification of iodine)
- radioactive I-131 or I-123 given PO to fasting patient
 - measure percentage of administered iodine taken up by thyroid
- increased RAIU: toxic multinodular goiter, toxic adenoma, Graves' disease
- decreased RAIU: subacute thyroiditis, late Hashimoto's disease, hormone suppression
- falsely decreased in patient with recent radiographic contrast studies, high dietary iodine (e.g. seaweed)

Thyroid Imaging (Scintiscan)

- Tc99m pertechnetate IV or radioactive iodine
- provides functional anatomic detail
- hot (hyperfunctioning) lesions
 - adenoma, toxic multinodular goiter
 - usually benign, cancer very unlikely (less than 1%)
- cold (hypofunctioning) lesions
 - cancer must be considered until biopsy negative even though only 6-10% are cancerous
- isointense lesions
 - cancer must be considered as an isointense lesion may represent cold nodules superimposed on normal tissue
 - if cyst suspected, correlate with U/S
- serum thyroglobulin to detect recurrent thyroid cancer post-treatment

Radioiodine Ablation

- I-131 for Graves' disease, multinodular goiter, thyroid cancer

Respiratory

V/Q Scan

- examine areas of lung in which ventilation and perfusion do not match
- ventilation scan
 - patient breathes radioactive gas through a closed system, filling alveoli proportionally to ventilation
 - ventilation scan defects indicate: airway obstruction, chronic lung disease, bronchospasm, tumour mass obstruction
- perfusion scan
 - radiotracer injected IV → trapped in pulmonary capillaries (1 in 1500 arterioles occluded) according to blood flow
 - gives a map of pulmonary circulation
 - relatively contraindicated in severe pulmonary HTN and right-to-left shunt
- with PE
 - areas of lung are well ventilated but not perfused (unmatched defect)
 - defects are wedge-shaped, extend to periphery, usually bilateral and multiple
 - reported as high probability, intermediate, low, very low, or normal
 - V/Q scans for PE have been largely replaced by CT scan with contrast (see [Respirology](#), R18)



V/Q Scan

For PE investigation: normal scan makes PE unlikely.
Probability of PE: high 80-100%, intermediate 20-80%, low <20%.



Ventilation Scan Defects indicate:

airway obstruction, chronic lung disease, bronchospasm, tumour mass obstruction.



Perfusion Scan Defects indicate:

reduced blood flow due to PE, COPD, asthma, bronchogenic carcinoma, inflammatory lung diseases (pneumonia, sarcoidosis), mediastinitis, mucous plug, vasculitis.

Cardiac

Myocardial Perfusion Scanning

- for investigation of angina, atypical chest pain, coronary artery disease (CAD), and follow-up post-bypass
- thallium-201 (a radioactive analogue of potassium), Tc99m MIBI, or Tc99m tetrofosmin
- injected at peak exercise (physical stress) or after persantine challenge (vasodilator) and again later at rest
- persistent defect (at rest and stress) suggests infarction; reversible defect (only during stress) suggests ischemia
- used to discriminate between reversible (ischemia) vs. irreversible (infarction) changes when other investigations are equivocal
- see [Cardiology and Cardiovascular Surgery](#), C10 for more details



Active uptake of radiolabel by myocardium is proportional to regional blood flow.



Persistent defect (at rest and stress) suggests infarction; reversible defect (only during stress) suggests ischemia.



MUGA Scan can be used to study the function of the heart at a particular stage of contraction. Superior to ECHO only in its reproducibility in EF measurement (precise).

Radionuclide Ventriculography

- Tc99m attached to red blood cells
- first pass through right ventricle → pulmonary circulation → left ventricle; provides information about RV function
- cardiac MUGA scan (Multiple Gated acquisition scan) sums multiple cardiac cycles
 - evaluation of LV function
 - images are obtained by gating (synchronizing) the count acquisitions to the ECG signal
 - MUGA scan can be used to study the function of the heart at a particular stage of contraction
- provides information on ejection fraction (normal = 50-65%), ventricular volume, and wall motion



Technetium pyrophosphate concentrates in bone and necrotic tissue.

Pyrophosphate Scintigraphy

- technetium pyrophosphate concentrates in bone and necrotic tissue
- used to detect infarcted tissue 1-5 days post-MI when ECG and enzyme results are equivocal or unreliable
- sensitivity and specificity about 90% for transmural infarct



Bone

Bone Scan

- isotopes
 - technetium Tc99m
 - ♦ triphasic bone scan: flow → blood pool → delayed bone images
 - ♦ uptake can distinguish bone vs. soft tissue infection and septic arthritis vs. osteomyelitis vs. peripheral cellulitis
 - ♦ acute osteomyelitis: increased activity in flow, blood pool, and delayed bone images; usually does not cross joint
 - ♦ septic arthritis and cellulitis: increased activity in blood pool and normal or slightly increased activity in delayed images; may cross joint
 - indium-111 WBC: tracks the active migration of the WBC, more specific for infection
 - gallium-67 citrate: may see uptake in some tumours, also more specific for infection
- radioactive tracer binds to hydroxyapatite of bone matrix
- increased binding when increased blood supply to bone and/or high bone turnover (active osteoblasts)
- differential diagnosis of positive bone scan:
 - bone metastases from breast, prostate, lung, thyroid
 - primary bone tumour
 - arthritis
 - fracture
 - infection
 - anemia
 - Paget's disease
- multiple myeloma: typically normal or cold (false negative); need a skeletal survey
- superscan: good visualization of bone, but not kidneys, due to diffuse metastases or metabolic causes (renal osteodystrophy)



Indications for a Bone Scan

- Bone pain of unknown origin
- AVN
- Suspected malignancy
- Staging malignancy (cancer of breast, prostate, kidney, thyroid or lung)
- Follow up after treatment
- Detection and follow up of primary bone disease
- Assessment of skeletal trauma
- Detection of soft tissue calcification
- Renal failure

Abdomen

HIDA (Hepatobiliary IminoDiacetic Acid) Scan

- IV injection of radiotracer (HIDA) which is bound to protein, taken up, and excreted by hepatocytes into biliary system
- can be performed in non-fasting state but prefer NPO after midnight
- gallbladder visualized when cystic duct is patent, usually seen by 30 min to 1 hour
- if gallbladder is not visualized, suspect obstructed cystic duct (acute or chronic cholecystitis)
- acute cholecystitis: no visualization of gallbladder at 4-hours or after administration of morphine at 30 minutes
- chronic cholecystitis: no visualization of gallbladder at 1-hour but seen at 4-hours or after morphine administration
- differential diagnosis of obstructed cystic duct: acute cholecystitis, decreased hepatobiliary function (commonly due to alcoholism), bile duct obstruction, parenteral nutrition, fasting less than 4 hours or more than 24 hours
- filling of gallbladder rules out cholecystitis (<1% probability)
- assess bile leaks post-operatively

RBC Scan

- IV injection of radiotracer with sequential images of the abdomen (Tc99m labeled RBCs)
- GI bleed
 - if bleeding acutely at <0.5 mL/min, the focus of activity in the images generally indicates the site of the acute bleed, look for a change in shape and location on sequential image
 - if bleeding acutely at >0.5 mL/min, use angiography (more specific)
 - RBC scan is more sensitive for lower GI bleed
- liver lesion evaluation
 - hemangioma has characteristic appearance: cold early, fills in later

Renal Scan

- see *Genitourinary System*, DM15

Inflammation and Infection

- gallium-67 citrate, indium-111, or Tc99m labeled WBCs
- gallium accumulates in skeleton, lacrimal glands, nasopharynx, normal liver, spleen, bone marrow, sites of inflammation, some neoplasms (lymphomas)
- labeled WBCs accumulate in normal spleen, liver, bone marrow, sites of inflammation and infection (abscess, sarcoid, osteomyelitis)

Brain

- SPECT Tc99m-HMPAO or Tc99m-ECD imaging assesses cerebral blood flow, taken up in cortical and subcortical grey matter; used for CVA, vasculitis, dementia
- PET imaging assesses metabolic activity by using 18-FDG
- CSF imaging, intrathecal administration of 111-In DTPA to evaluate CSF leak or to differentiate normal pressure hydrocephalus from other causes of hydrocephalus

Interventional Radiology

Vascular Procedures

Angiography

- injection of contrast material through a catheter placed directly into an artery (or vein) to delineate vascular anatomy
- catheter can be placed into a large vessel (e.g. aorta, vena cava) for a “flush” or selectively placed into a branch vessel for more detailed examination of smaller vessels and specific organs
- **indications:** diagnosis of primary occlusive or stenotic vascular disease, aneurysms, coronary, carotid and cerebral vascular disease, PE, trauma, bleeding (GI, hemoptysis, hematuria), vascular malformations, as part of endovascular procedures (EVAR, thrombolysis, stenting and angioplasties)
- **complications:** puncture site hematoma, infection, pseudoaneurysm, AV fistula, dissection, thrombosis, embolic occlusion of a distal vessel
- significant complications occur in $<5\%$ of patients
- due to improved technology, non-invasive evaluation of vascular structures is being performed more frequently (colour Doppler U/S, CT angiography and MR angiography)
- see *Neuroradiology*, DM17 and *Angiography of GI Tract*, DM15

Percutaneous Transluminal Angioplasty (PTA) and Stents

- introduction and inflation of a balloon into a stenosed vessel to restore distal blood supply
- common alternative to surgical bypass grafting with five year patency rates similar to surgery, depending on site
- renal, iliac, femoral, mesenteric, subclavian, coronary and carotid artery stenoses are amenable to treatment
- vascular stents may help improve long term results by keeping the vessel wall patent after PTA
- stents are also used for angioplasty failure or complications
- covered stents (a.k.a. stent grafts) may provide an alternative treatment option for aneurysms and AV fistulas
- **complications:** similar to angiography, but also includes vessel rupture

Thrombolytic Therapy

- may be systemic (IV) or catheter directed
- infusion of a fibrinolytic agent (urokinase, streptokinase, TNK, tPA – used most commonly) via a catheter inserted directly into a thrombus
- can restore blood flow in a vessel obstructed with a thrombus or embolus
- **indications:** treatment of ischemic limb (most common indication), early treatment of MI or stroke to reduce organ damage, treatment of venous thrombosis (DVT or PE)
- **complications:** bleeding, stroke, distal embolus, reperfusion injury with myoglobinuria and renal failure if advanced ischemia present

**Contraindications to Intravascular Contrast Media**

- Anaphylactic reaction
- Multiple myeloma
- Dehydration
- Diabetes

Relative Contraindications

- Renal failure
- Severe heart failure

Thrombolytic Therapy for Pulmonary Embolism
Cochrane Database of Systematic Reviews 2009, Issue 3

Study: Systematic review of randomized controlled trials comparing thrombolytic therapy with placebo, heparin, or surgical intervention.

Patients: 679 patients with acute PE.

Intervention: Thrombolytics vs. heparin or placebo.

Outcome: Death rate, recurrence of PE, major and minor hemorrhagic events.

Results: Non-significant difference between thrombolytics and heparin or placebo in all measured outcomes. Rt-PA and heparin together reduced need for treatment for in-hospital events. Thrombolytics improved hemodynamic outcome, lung VQ scans, pulmonary angio assessment and echocardiograms greater than heparin. Need for further double-blinded RCTs.



Advanced ischemia patients should receive surgery rather than thrombolysis.



Indications for Central Venous Access
FAT CAB
 Fluids
 Antibiotics
 TPN
 Chemotherapy
 Administration of blood
 Blood sampling



Figure 22. Retrievable IVC Filter



Figure 23. Femoral Arteriogram
 – showing distal occlusion of
 superficial femoral artery



ERCP is the primary modality for distal
 common bile duct obstructions.

Embolization

- injection of occluding material into vessels
- permanent agents: coils, balloons, glue
- temporary: gel foam, autologous blood clots
- **indications:** management of hemorrhage (epistaxis, trauma, GI bleed, GU bleed), treatment of AVM, pre-operative treatment of vascular tumours (bone metastases, renal cell carcinoma), varicocele embolization for infertility, symptomatic uterine fibroids
- **complications**
 - post embolization syndrome (pain, fever, leukocytosis)
 - unintentional embolization of a non-target organ with resultant ischemia

Inferior Vena Cava Filter

- insertion of metallic “umbrellas” to mechanically trap emboli and prevent PE
- may be temporary (retrievable) or permanent
- inserted via femoral vein, jugular vein, or antecubital vein
- usually placed infrarenally to avoid renal vein thrombosis
- **indications:** contraindication to anticoagulation, failure of adequate anticoagulation (e.g. recurrent PE despite therapeutic anticoagulant levels), complication of anticoagulation

Central Venous Access

- variety of devices available
 - peripherally inserted central catheter (PICC), external tunneled catheter (Hickmann or dialysis catheters), subcutaneous port (Portacath®)
- **indications:** chemotherapy, TPN, long-term antibiotics, administration of fluids and blood products, blood sampling
- **complications:** venous thrombosis and central venous stenosis, infection including sepsis, pneumothorax

Nonvascular Interventions

Percutaneous Biopsy

- replaces open surgical procedure
- many sites are amenable to biopsy using U/S, fluoroscopy or CT guidance
- **complications**
 - false negative biopsies due to sampling error or tissue necrosis
 - pneumothorax in 30% of lung biopsies, chest tube required in approximately 5%
 - pancreatic biopsies are associated with risk of inducing acute pancreatitis
 - transjugular liver biopsies can be performed to minimize bleeding complications in patients with uncorrectable coagulopathies or ascites

Abscess Drainage

- placement of a drainage catheter into an infected fluid collection
- administer broad spectrum IV antibiotics prior to procedure
- routes: percutaneous (most common), transgluteal, transvaginal, transrectal
- **complications**
 - hemorrhage
 - injury to intervening structures (e.g. bowel)
 - bacteremia, sepsis

Percutaneous Biliary Drainage (PBD)/Cholecystostomy

- placement of drainage catheter ± metallic stent into obstructed biliary system (PBD) or gallbladder (cholecystostomy) for relief of jaundice or infection
- percutaneous gallbladder access can be used to crush or remove stones
- **indications**
 - cholecystostomy: acute cholecystitis
 - percutaneous biliary drainage: biliary obstruction secondary to stone or tumour, cholangitis
- **complications**
 - acute: sepsis, hemorrhage
 - long-term: tumour overgrowth and stent occlusion

Percutaneous Nephrostomy

- placement of catheter into renal collecting system
- **indications:** hydronephrosis (urinary obstruction as a result of a stone or tumour), pyonephrosis, ureteric injury with or without urinary peritonitis (traumatic or iatrogenic)
- **complications:** bacteria and septic shock, hematuria due to pseudoaneurysm or AV fistulas, injury to adjacent organs

Gastrostomy/Gastrojejunostomy

- percutaneous placement of catheter directly into either stomach (gastrostomy) or through stomach into small bowel (transgastric jejunostomy)
- **indications**
 - feeding: inability to eat (most commonly CNS lesion, e.g. stroke) or esophageal obstruction
 - decompression: gastric outlet obstruction
- **complications:** gastroesophageal reflux with aspiration, peritonitis, hemorrhage, bowel or solid organ injury

Radiofrequency (RF) Ablation

- U/S or CT guided probe is inserted into tumour, RF energy delivered through probe causes heat deposition and tissue destruction
- **indications:** hepatic tumours (hepatocellular carcinoma and metastases), renal tumours
- **complications:** destruction of neighbouring tissues and structures, bleeding

Women's Imaging

Modalities

MAMMOGRAPHY**Description**

- x-ray imaging of the breasts for screening in asymptomatic patients, or diagnosis of clinically-detected or screening-detected abnormalities

Indications

- screening
 - begin screening from age 40 or 50 at one to two-year intervals
 - if over the age of 70, continue screening mammography if in good general health
 - not routinely recommended if under the age of 40 unless strong family history
 - begin 5-10 years younger than the first degree relative who developed breast cancer
- diagnostic
 - signs and symptoms suggestive of breast cancer including a lump or thickening, localized nodularity, dimpling or contour deformity, a persistent focal area of pain, and spontaneous serous or sanguinous nipple discharge from a single duct
 - women with abnormal screening mammograms
 - follow-up of women with previous breast cancer
 - suspected complications of breast implants

BREAST MRI**Description**

- breast MRI should be used only after mammography and ultrasound investigation
- sensitive for detecting invasive breast cancer (95-100%) but not specific (37-97%)
- use as a screening modality has been limited to high risk patients

Indications

- evaluation of diagnosed breast cancer: positive margins, recurrence, response to chemotherapy
- post-surgical resection of breast cancer
- known BRCA1 or BRCA2 mutation, or other gene predisposing to breast cancer
- untested first-degree relative of a carrier of such a gene mutation
- family history consistent with a hereditary breast cancer syndrome and estimated personal lifetime cancer risk >25%
- high-risk marker on prior biopsy (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ)
- radiation therapy to chest (before age 30)
- NOTE: MRI should not be used to screen the general population or to differentiate between benign and malignant lesions

ULTRASOUND

Definition

- ultrasound can determine if a mass is cystic or solid and is commonly used during biopsy

Indications

- identification and characterization of palpable abnormalities
- evaluation of ambiguous mammographic findings in the determination of cystic versus solid characteristics
- evaluation of patients with suspected silicone implant rupture and problems associated with breast implants
- guidance for interventional procedures
- breast sonography is the initial imaging technique to evaluate palpable masses in women under 30 and in lactating and pregnant women

BREAST INTERVENTIONAL PROCEDURES

Description

- breast interventional procedures include FNA biopsy, core needle biopsy, abscess drainage, and cyst aspiration

Indications

- cystic mass: complex cyst, symptomatic, suspected abscess
- solid mass: confirm diagnosis of a lesion suspicious for malignancy (BI-RADS® Category 4 or 5) or confirm diagnosis of a probably benign mass (BI-RADS® Category 3)
- initial percutaneous biopsy procedure that was insufficient or discordant with imaging
- presurgical ultrasound-guided localization of a lesion

Breast Imaging Reporting

Breast Imaging Reporting and Data System (BI-RADS®)

- a widely accepted standardized reporting system for breast imaging published by the American College of Radiology

Format of Report

1. indication for exam
2. breast composition
3. finding(s)
4. comparison to previous studies (if available)
5. overall assessment

Breast Composition

- dense breast tissue makes it difficult to separate normal gland tissue from tumours
- BI-RAD system grades composition of breast tissue
 - almost entirely fatty: mammography very effective, sensitive to even small tumours
 - scattered fibroglandular tissue: minor decrease in sensitivity
 - heterogeneously dense tissue: moderate decrease in sensitivity
 - extremely dense tissue: marked decrease in sensitivity

Overall Assessment Categories

- Category 0 – need additional imaging evaluation: technically unsatisfactory scan or when more information is needed to interpret the scan (e.g. prior imaging, correlation with history)
- Category 1 – negative: nothing to comment on; breasts are symmetrical, no masses, architectural disturbances, or suspicious calcifications are present; routine follow-up advised
- Category 2 – benign finding: negative mammogram with benign findings (e.g. calcifications, lipoma, lymph nodes)
- Category 3 – probably benign finding: short interval follow-up suggested
- Category 4 – suspicious abnormality: biopsy should be considered
 - Category 4A may be used for a finding needing intervention but with a low suspicion for malignancy
 - Category 4B includes lesions with an intermediate suspicion of malignancy and warrants close radiologic and pathologic correlation
 - Category 4C includes findings of moderate concern, but not classic (as in Category 5) for malignancy; malignant result in this category is expected
- Category 5 – highly suggestive of malignancy: appropriate action should be taken
- Category 6 – known biopsy-proven malignancy: appropriate action should be taken; a cancer diagnosis that has been established by histology is imaged and corresponds to the previously biopsied lesion

Breast Findings

Breast Masses

- definition: a space occupying lesion seen in two different projections; if seen in only a single projection it should be called a "density" until its three-dimensionality is confirmed
 - when a density is seen on one view, additional views must be done to confirm or exclude the presence of a mass; this may mean asking the patient to return
- shape: oval, round, or lobular suggests benign; irregular is more concerning for malignancy
- margin: indistinct, microlobulated, or frankly speculated (radiating lines) margins suggest infiltration; circumscribed, well-defined margins are reassuring; may require focal magnification mammogram to fully characterize margin
- density: higher density than surrounding tissue is suspicious for malignancy; radiolucent lesions are fat-containing and may be an oil cyst, lipoma, galactocele, hamartoma or fibrolipoma

Architectural Distortion

- definition: the normal architecture is distorted with no definite mass visible; this includes spiculations radiating from a point, and focal retraction or distortion of the edge of the parenchyma; may be concerning for malignancy or occur with healing after injury (including previous biopsy)
- spiculations (lines radiating from the centre)
- retraction (puckering) of normal connective tissues lines

Calcifications

- size: benign calcifications are usually larger than calcifications associated with malignancy
- shape: benign lesions are often round with smooth margins and are much more easily seen; hazy "flake" shaped lesions are indeterminate; thin, irregular, and branched suggest malignancy
- distribution: regional, scattered, and diffuse calcifications suggest benign; grouped, linear or segmental calcifications are suspicious for malignancy
- typically benign forms:
 - skin calcifications: lucent-centred and benign
 - vascular calcifications: parallel paired tracks or linear tubular calcifications clearly associated with calcification of small arteries
 - coarse or popcorn-like calcifications: classic rounded groups of coarse calcifications develop in an involuting fibroadenoma
 - large rod-shaped calcifications: benign calcifications forming continuous rods that may occasionally branch; usually more than 1 mm in diameter, may have lucent centre if calcium surrounds rather than fills an enlarged duct; found in secretory disease, plasma cell mastitis, and duct ectasia
 - round calcifications: usually considered benign and when small (under 1 mm), the term punctate may be used; smooth, dense, and round
 - spherical or lucent-centred calcifications: benign calcifications that range from under 1 mm to over a centimeter; smooth surfaces, round or oval, tend to have a lucent centre; arise from areas of fat necrosis, calcified duct debris, and occasionally fibroadenoma

Intermediate Concern Calcifications

- amorphous or indistinct calcifications: round or "flake" shaped calcifications that are sufficiently small or hazy in appearance that a more specific morphologic classification cannot be determined; biopsy may be necessary

Calcifications of High Probability of Malignancy

- pleomorphic or heterogeneous calcifications (granular): usually more conspicuous than amorphous forms, but are neither characteristic of a benign calcification, nor typically malignant; irregular calcifications of varying size and shape, usually less than 0.5 mm in size
- fine and/or branching (casting) calcifications: thin, irregular calcifications that appear linear, but are discontinuous and under 0.5 mm in width; their appearance suggests filling of the lumen of a duct involved irregularly by breast cancer

Other Findings

- tubular density/dilated duct: branching tubular structures usually represent enlarged ducts (milk ducts); if they are clearly identified as such, these densities are of little concern
- intramammary lymph node: typical lymph nodes are circumscribed, reniform and often have a fatty notch and centre; usually less than 1 cm, and usually seen in the outer, often upper part of the breast; when these characteristics (particularly fatty centre or notch) are well seen, the lesion is almost always benign and insignificant
- focal asymmetric density: area of breast density with similar shape on two views, but completely lacking borders and conspicuity of a true mass; must be carefully evaluated with focal compression to exclude findings of a true mass or architectural distortion
 - if focal compression shows mass-like character, or if the area can be palpated, biopsy must be considered

References

- American College of Radiology (ACR) Breast Imaging Reporting and Data System Atlas (BI-RADS Atlas). Reston, Va: American College of Radiology; 2003
- Brant WE, Helms CA (1999). Fundamentals of diagnostic radiology. Philadelphia. Lippincott Williams and Wilkins.
- Canadian Association of Radiologists (CAR) Standard for Breast Imaging. Ottawa, ON. Canadian Association of Radiologists. 1998.
- Canadian Association of Radiologists (CAR) Standard for Performance of Breast Ultrasound Examination. Ottawa, ON. Canadian Association of Radiologists. 2003.
- Canadian Association of Radiologists (CAR) Standards for the Performance of Ultrasound-Guided Percutaneous Breast Interventional Procedures. Ottawa, ON. Canadian Association of Radiologists. 2003.
- Chen MYM, Pope, TL, Ott DJ. (2004) Basic Radiology. New York. Lange Medical Books/McGraw Hill.
- Daffner RH (1993). Clinical radiology: the essentials. Baltimore: Williams & Wilkins.
- Erkonen WE, Smith WL. (2005). Radiology 101. Philadelphia: Lippincott Williams & Wilkins.
- Fleckenstein P, Tranun-Jensen J (2001). Anatomy in Diagnostic Imaging. 2nd ed. Copenhagen: Blackwell Publishing.
- Gay S, Woodcock Jr RJ (2000). Radiology Recall. Baltimore: Lippincott Williams & Wilkins.
- Goodman LR (2007). Felson's Principles of Chest Roentgenology: A Programmed Text. 3rd ed. Philadelphia: Saunders.
- Joffe SA, Servaes S, Okon S, Horowitz M. Multi-detector row CT urography in the evaluation of hematuria. Radiographics. 2003, 23(6):1441-55.
- Juhl JH, Crummy AB, Kuhlman JE (1998). Paul and Juhl's Essentials of Radiologic Imaging. Philadelphia: Lippincott-Raven.
- Katz DS, Math KR, Groskin SA (1998). Radiology secrets. Philadelphia: Hanley and Belfus.
- Mettler FA Jr, Huda W, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology. 2008;248(1):254-63.
- Novelline RA (2004). Squire's Fundamentals of Radiology. 6th ed. Cambridge:Harvard.
- Ouellette H, Tetreault P. (2002). Clinical Radiology made ridiculously simple. Miami: MedMaster.
- Sam PM, Curtin HD (1996). Head and neck imaging. 3rd ed.. St. Louis: Mosby.
- Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Magnetic Resonance imaging screening of women at high risk for breast cancer : a clinical practice guideline. Cancer Care Ontario's Program in Evidence-based Care. 2007.
- Weissleder R, Rieumont MJ, Wittenberg J. (1997) Primer of Diagnostic Imaging. 2nd ed. Philadelphia: Mosby.

Mike Romano, John Sauve and Ryan Zufelt, chapter editors

Christopher Kitamura and Michelle Lam, associate editors

Janine Huston, EBM editor

Dr. Simon Kingsley, staff editor

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Initial Patient Assessment/Management

1. Rapid Primary Survey (RPS)



Approach to the Critically Ill Patient

1. Rapid Primary Survey (RPS)
2. Resuscitation (often concurrent with RPS)
3. Detailed Secondary Survey
4. Definitive Care



Noisy breathing is obstructed breathing until proven otherwise.



Signs of Airway Obstruction

- Agitation, confusion, "universal choking sign"
- Respiratory distress
- Failure to speak, dysphonia
- Cyanosis



Medications that can be Delivered via ETT

NAVEL

- Naloxone (Narcan)
- Atropine
- Ventolin (Salbutamol)
- Epinephrine
- Lidocaine



Indications for Intubation

- Unable to protect airway (e.g. Glasgow Coma Scale (GCS) <8; airway trauma)
- Inadequate oxygenation with spontaneous respiration (O_2 saturation <90% with 100% O_2 or rising pCO_2)
- Profound shock
- Anticipatory: in trauma, overdose, congestive heart failure (CHF), asthma, chronic obstructive pulmonary disease (COPD) and smoke inhalation injury
- Anticipated transfer of critically ill patients



Added Equipment and Techniques in Intubation

- Bougie (used like a guidewire)
- Retrograde intubation (ETT threaded over a wire inserted through skin and out mouth)
- Lighted stylet (use light through skin to determine if ETT in correct place)
- Fiberoptic intubation – indirect vision using fiberoptic cable

- Airway maintenance with cervical spine (C-spine) control

- Breathing and ventilation

- Circulation (pulses, hemorrhage control)

- Disability (neurological status)

- Exposure (complete) and Environment (temperature control)

- Continually reassessed during secondary survey

IMPORTANT: always watch for signs of shock while doing primary survey (see Table 1)

A. AIRWAY

- first priority is to secure airway

- assume a cervical injury in every trauma patient and immobilize with collar

- assess ability to breathe and speak

- can change rapidly, therefore reassess frequently

Airway Management

- goals

- permit adequate oxygenation and ventilation

- facilitate ongoing patient management

- give drugs via endotracheal tube (ETT) if IV not available

- Note: start with basic management techniques before progressing to advanced (see below)

1. Basic Airway Management (Temporizing Measures)

- protect the C-spine

- head-tilt (if C-spine injury not suspected) or jaw thrust to open the airway

- sweep and suction to clear mouth of foreign material

2. Definitive Airway Management

- ETT intubation with inline stabilization of spine (Figure 1)

- orotracheal ± Rapid Sequence Intubation (RSI) preferred

- nasotracheal – may be better tolerated in conscious patient

- ♦ relatively contraindicated with basal skull fracture

- does not provide 100% protection against aspiration

- surgical airway (if unable to intubate using oral/nasal route and unable to ventilate)

- cricothyroidotomy

3. Rescue or Temporizing Measures

- nasopharyngeal airway

- oropharyngeal airway (not if gag reflex present)

- "rescue" airway devices (e.g. laryngeal mask airway (LMA); Combitube®)

- transtracheal jet ventilation through cricothyroid membrane (last resort)

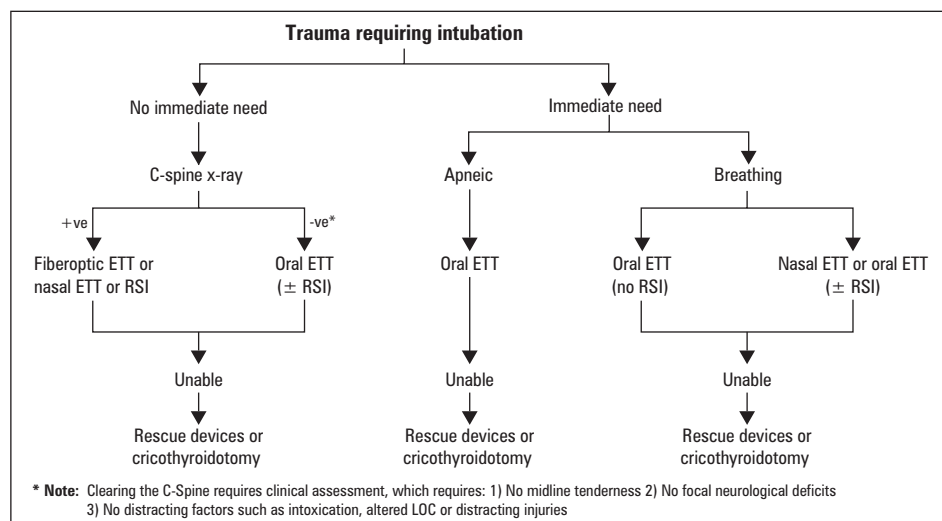


Figure 1. Approach to Endotracheal Intubation in an Injured Patient

ETT – endotracheal tube intubation; RSI – rapid sequence intubation

B. BREATHING

- **Look**
 - mental status (anxiety, agitation, decreased LOC), colour, chest movement (bilateral vs. asymmetrical), respiratory rate/effort, nasal flaring
- **Listen**
 - sounds of obstruction (e.g. stridor), breath sounds, symmetry of air entry, air escaping
- **Feel**
 - flow of air, tracheal shift, chest wall for crepitus, flail segments, sucking chest wounds, subcutaneous emphysema

Breathing Assessment

- measurement of respiratory function: rate, pulse oximetry, arterial blood gas (ABG), A-a gradient

Management of Breathing

- nasal prongs → simple face mask → oxygen reservoir → CPAP/BiPAP
- Venturi mask: used to precisely control O₂ delivery
- Bag-Valve mask and CPAP to supplement ventilation

C. CIRCULATION

Definition of Shock

- inadequate organ and tissue perfusion with oxygenated blood (brain, kidney, extremities) (see Table 2)

Table 1. Major Types of Shock

Hypovolemic	Cardiogenic	Distributive (vasodilation)	Obstructive
Hemorrhage (external and internal)	Myocardial Ischemia	Septic	Cardiac tamponade
Severe burns	Arrhythmias	Anaphylactic	Tension pneumothorax
High output fistulas	Congestive Heart Failure	Neurogenic (spinal cord injury)	Pulmonary embolism
Dehydration (diarrhea, DKA)	Cardiomyopathies		Aortic stenosis
	Cardiac valve problems		Constrictive pericarditis

Clinical Evaluation

- early: tachypnea, tachycardia, narrow pulse pressure, reduced capillary refill, cool extremities and reduced central venous pressure (CVP)
- late: hypotension and altered mental status, reduced urine output

Table 2. Estimation of Degree of Hemorrhagic Shock

Class	I	II	III	IV
Blood Loss	<750 cc	750-1500 cc	1500-2000 cc	>2000 cc
% of blood volume	<15%	15-30%	30-40%	>40%
Pulse	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Respiratory rate	20	30	35	>45
Capillary refill	Normal	Decreased	Decreased	Decreased
Urinary output	30 cc/hr	20 cc/hr	10 cc/hr	None
Fluid replacement	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

Management of Hemorrhagic Shock

- secure airway and supply O₂
- **TREAT THE CAUSE OF THE SHOCK**
- control external bleeding
 - direct pressure
 - elevate extremities if no obvious unstable fracture
 - consider vascular pressure points (brachial, axillary, femoral)
 - do not remove impaled objects as they tamponade bleeding
 - tourniquet only as last resort
- prompt surgical consultation for active internal bleeding
- infusion of 1-2 L of NS/RL as rapidly as possible → 2 large bore (14 gauge) IVs wide open
- warm blood/IV fluids, especially for massive transfusions
- replace lost blood volume at ratio of 3:1 with crystalloid
- if inadequate response, consider ongoing blood loss (e.g. chest, abdomen, pelvis, extremities) → operative intervention required
- indications for blood transfusion
 - severe hypotension on arrival
 - shock persists following crystalloid infusion
 - rapid bleeding



Shock in a trauma patient is hemorrhagic until proven otherwise.



Causes of Shock

SHOCKED

Septic, Spinal/neurogenic, Hemorrhagic
 Obstructive (e.g. tension pneumothorax, cardiac tamponade, pulmonary embolism)
 Cardiogenic (e.g. blunt myocardial injury, arrhythmia, MI)
 anaphylactic
 Endocrine (e.g. Addison's, myxedema, coma)
 Drugs



Estimated Systolic Blood Pressure Based on Position of Most Distal Palpable Pulse

	sBP (mmHg)
Radial	>80
Femoral	>70
Carotid	>60



Hemorrhage Management

RED

Rest

Elevate the bleeding area above the level of the heart if possible
 Direct pressure on the bleeding site



Fluid Resuscitation

Give bolus until HR decreases, urine output picks up, and patient stabilizes
 Maintenance: 4-2-1 rule
 first 10kg: 4cc/kg/hr
 10-20kg: 2cc/kg/hr
 remaining weight: 1cc/kg/hr
 replace ongoing losses and deficits (assume 10% of body weight)



Since only 30% of infused isotonic crystalloids remains in intravascular space, you must give 3x estimated blood loss.



Initial Management of Any Patient in Shock

ABCs
IV fluids
Oxygen
Monitor (HR, BP, urine, mentation, O₂ sat.)
Control hemorrhage



Method of Assessing Level of Consciousness

AVPU

Alert
Responds to Verbal stimuli
Responds to Painful stimuli
Unresponsive



Unproven or Harmful Treatments for Hemorrhage Shock

- Trendelenburg position
- Steroids (used only in spinal cord injury)
- MAST garments
- Vasopressors

Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

NEJM 2008; 358:877-87

Study: Multicenter, randomized, double-blind trial
Patients: 778 patients with septic shock

Intervention: Low-dose vasopressin (0.01 to 0.03 U per minute) or norepinephrine (5 to 15 ug per minute) in addition to open-label vasopressors and a minimum of 5ug of norepinephrine.

Outcome: Mortality rate 28 days after start of infusions.

Results: No significant difference between the vasopressin and the norepinephrine groups at 28 days or 90 days. However, in patients with less severe septic shock, mortality rate was lower in the vasopressin group.



Foley Contraindications

- Blood at urethral meatus
- Scrotal hematoma
- High-riding prostate on DRE



NG Tube Contraindications

- Significant mid-face trauma
- Basal skull fracture

- transfusion options with packed red blood cells (pRBCs)
 - crossmatched if possible
 - type-specific (provided by most blood banks within 10 minutes)
 - ♦ preferred to O-negative un-crossmatched blood if both available
 - O-negative (children and women of child-bearing age)
 - O-positive if no time for cross-match (males/postmenopausal women)
 - anticipate complications with massive transfusions
 - consider replacement of other blood products (platelets, FFP) after 2-4 units pRBCs
- transfusion with fresh frozen plasma (FFP)
 - used for clinical evidence of impaired hemostasis
 - ongoing hemorrhage, PT >1.5x normal range

D. DISABILITY

- assess level of consciousness by AVPU method (see sidebox) or GCS

Glasgow Coma Scale (GCS)

- for use in trauma patients with decreased LOC; good indicator of severity of injury and neurosurgical prognosis
- may be used for metabolic coma, but less meaningful
- most useful if repeated and used for monitoring of trend
 - change in GCS with time is more relevant than the absolute number
 - patient with deteriorating GCS needs immediate attention
 - prognosis based on **best post-resuscitation** GCS
- reported as a 3 part score: Eyes + Verbal + Motor = Total (see Table 3)
- if patient intubated, GCS score reported out of 10 + T (T= tubed, i.e. no verbal component)

Table 3. Glasgow Coma Scale

Eyes Open		Best Verbal Response		Best Motor Response	
Spontaneously	4	Answers questions appropriately	5	Obeys commands	6
To voice	3	Confused, disoriented	4	Localizes to pain	5
To pain	2	Inappropriate words	3	Withdraws from pain	4
No response	1	Incomprehensible sounds	2	Decorticate (flexion)	3
		No verbal response	1	Decerebrate (extension)	2
				No response	1

13-15 = mild injury, 9-12 = moderate injury, ≤8 = severe injury

See Table 28 for modified GCS for infants and children

E. EXPOSURE/ENVIRONMENT

- undress patient completely and assess entire body for injury; logroll to examine back
- digital rectal exam
- keep patient warm with a blanket ± radiant heaters; avoid hypothermia
- warm IV fluids/blood
- keep providers safe (contamination, combative patient)

2. Resuscitation

- done simultaneously with primary survey
- attend to ABCs (see Table 4)
- manage life-threatening problems as they are identified
- vital signs q5-15 minutes
- ECG, BP and O₂ monitors
- Foley catheter and nasogastric (NG) tube if indicated
- tests and investigations: CBC, electrolytes, BUN, Cr, glucose, amylase, INR/PTT, β-hCG, toxicology screen, cross and type

Table 4. 2005 AHA CPR Guidelines

Step/Action	Adult: >8yrs	Child: 1-8 years	Infant: <1 year
Airway	Head tilt-chin lift		
Breaths	2 breaths at 1 second/breath		
Foreign-body airway obstruction	Abdominal thrust		Back slaps and chest thrusts
Compressions			
Compression landmarks	In the centre of the chest, between nipples		Just below nipple line
Compression method: push hard and fast and allow for complete recoil	2 Hands: Heel of 1 hand, second hand on top	2 Hands: Heel of 1 hand with second on top, or 1 Hand: Heel of 1 hand only	2 fingers
Compression depth	1 ½ to 2 inches	About ⅓ to ½ the depth of the chest	
Compression rate	100/min		
Compression-ventilation ratio	30 compressions to 2 ventilations		
Compression-only CPR	Hands-only CPR is preferred if the bystander is not trained or does not feel confident in their ability to provide conventional CPR or if the bystander is trained but chooses to use compressions-only		
Defibrillation	Immediate defibrillation for all rescuers responding to a sudden witnessed collapse. Compression (5cycles/2min) before AED is considered if EMS arrival is > 4-5 minutes after the call		No defibrillation

3. Detailed Secondary Survey

- done after rapid primary survey problems have been addressed
- identifies major injuries or areas of concern
- full physical exam and x-rays (C-spine, chest, pelvis – required in blunt trauma, consider T-spine and L-spine)

HISTORY

- “SAMPLE”: Signs and Symptoms, Allergies, Medications, Past medical history, Last meal, Events related to injury

PHYSICAL EXAMINATION

Head and Neck

- pupils
 - assess equality, size, symmetry, reactivity to light
 - ♦ inequality/sluggish suggests local eye problem or lateralizing CNS lesion
 - ♦ relative afferent pupillary defect (swinging light test) – optic nerve damage
 - ♦ extraocular movements and nystagmus
 - ♦ fundoscopy (papilledema, hemorrhages)
 - reactivity/level of consciousness (LOC)
 - reactive pupils + decreased LOC → metabolic or structural cause
 - non-reactive pupils + decreased LOC → structural cause (especially if asymmetric)
- palpation of facial bones, scalp

Chest

- inspect for midline trachea, flail segment: ≥2 rib fractures in ≥2 places; if present look for associated hemothorax, pneumothorax, and contusions
- auscultate lung fields
- palpate for subcutaneous emphysema

Abdomen

- assess for peritonitis, abdominal distention, and evidence of intra-abdominal bleeding
- FAST (Focused Abdominal Sonogram in Trauma), diagnostic peritoneal lavage (DPL) or CT
- rectal exam for GI bleed, high riding prostate and anal tone (best to do during the log roll)
- bimanual exam in females as appropriate

Musculoskeletal (MSK)

- examine all extremities for swelling, deformity, contusion, tenderness, range of motion
- check for pulses and sensation in all injured limbs
- log roll and palpate thoracic and lumbar spines
- palpate iliac crests and pubic symphysis, pelvic stability (lateral, AP, vertical)



Unilateral, Dilated, Non-reactive Pupil, Think:
Focal mass lesion
Epidural hematoma
Subdural hematoma



Non-contrast head CT is the best imaging modality for intracerebral injury.



Signs of Increased Intracranial Pressure (ICP)

- Deteriorating LOC (hallmark)
- Deteriorating respiratory pattern
- Cushing reflex (high BP, low heart rate, irregular respirations)
- Lateralizing CNS signs (e.g. cranial nerve palsies, hemiparesis)
- Seizures
- Papilledema (occurs late)
- N/V and H/A

Neurological

- GCS
- full cranial nerve exam
- alterations of rate and rhythm of breathing are signs of structural or metabolic abnormalities
 - progressive deterioration of breathing pattern implies a failing CNS
- assess spinal cord integrity
 - conscious patient: assess distal sensation and motor
 - unconscious patient: response to painful or noxious stimulus applied to extremities

4. Definitive Care

- continue therapy
- continue patient evaluations and special investigations
- specialty consultations including OR as needed
- disposition: home, admission, or transfer to another setting (e.g. OR, ICU)

Ethical Considerations**Consent to Treatment: Adults**

- Emergency Rule: consent is not needed when patient is at imminent risk from a serious injury (e.g. severe suffering, loss of limb, vital organ or life) AND obtaining consent is either: a) not possible (e.g. patient is comatose); OR b) would increase risk to the patient (e.g. time delay)
 - assumes that most people would want to be saved in an emergency
- any capable and informed patient can refuse treatment, even if it is life-saving
 - consider: is the patient truly capable? Does pain, stress, or psychological distress impair their judgment?
- exceptions to the Emergency Rule: treatment cannot be initiated if
 - a competent patient has previously refused the same or similar treatment and there is no evidence to suggest the patient's wishes have changed
 - an advance directive is available – e.g. do not resuscitate (DNR) order
- refusal of help in a suicide situation is not an exception; care must be given
- if in doubt, initiate treatment
 - care can be withdrawn if appropriate at a later time or if wishes clarified by family

Consent to Treatment: Children

- treat immediately if patient is at imminent risk
- parents/guardians have the right to make treatment decisions
- if parents refuse treatment that is life-saving or will potentially alter the child's quality of life, Children's Aid Society (CAS) must be contacted – consent of CAS is needed to treat

Other Issues of Consent

- need consent for HIV testing, as well as for administration of blood products

Duty to Report

- law may vary depending on province and/or state
 - gunshot wounds, potential drunken drivers, suspected child abuse, various communicable diseases
 - medical unsuitability to drive

Traumatology

- epidemiology
 - leading cause of death in patients <45 yrs
 - 4th highest cause of death in North America
 - causes more deaths in children/adolescents than all diseases combined
- trimodal distribution of death
 - minutes: lethal injuries, death usually at the scene
 - early: death within 4-6 hours – “golden hour” (but decreased mortality with trauma care)
 - days-weeks: death from multiple organ dysfunction, sepsis, etc.
- injuries generally fall into two categories
 - blunt (most common): motor vehicle collision (MVC), pedestrian-automobile impact, motorcycle collision, fall, assault, sports
 - penetrating (increasing in incidence): gunshot wound, stabbing, impalement

Considerations for Traumatic Injury

- important to know the mechanism of injury in order to anticipate traumatic injuries
- always look for an underlying cause (alcohol, medications, illicit substances, seizure, suicide attempt, medical problem)
- always inquire about head injury, loss of consciousness, amnesia, vomiting, headache and seizure activity

**Jehovah's Witnesses**

- Capable adults have the right to refuse medical treatment
- May refuse whole blood, pRBCs, platelets and plasma even if life-saving
- Should be questioned directly about the use of albumin, immunoglobulins, hemophilic preparations
- Do not allow autologous transfusion unless there is uninterrupted extra corporeal circulation
- Usually ask for the highest possible quality of care without the use of the above interventions (e.g. crystalloids for volume expansion, attempts at bloodless surgery)
- Patient will generally sign hospital forms releasing medical staff from liability
- Most legal cases involve children of Jehovah's Witnesses; if life-saving treatment is refused contacted CAS

**High Risk Injuries**

- MVC at high speed, resulting in ejection from vehicle
- Motorcycle collisions
- Vehicle vs. pedestrian crashes
- Fall from height > 12 ft (3.6 m)

Motor Vehicle Collision (MVC)

- vehicle(s) involved: weight, size, speed, amount of damage
- type of crash (to assess location of possible injuries)
 - lateral/T-bone and head-on: head, cervical spine, thoracic, abdominal, pelvic and lower extremity
 - rear-end: hyper-extension of cervical spine (whiplash injury to neck)
 - roll over: energy dissipated, less likely severe injury if victim restrained by seatbelt, however still significant potential morbidity
- location of patient in vehicle
- use and type of seatbelt
 - lap belt: spine and abdominal injury
 - shoulder belt: look for major vessel injury
- ejection of patient from vehicle/entrapment of patient under vehicle
- airbag deployment
- use of helmet in motorcycle or bicycle collisions

Pedestrian-Automobile Impact

- high morbidity and mortality
- vehicle speed is an important factor
- site of impact on car
 - children tend to be run over
 - adults tend to be struck in lower legs, impacted again on car (truncal injury) and thrown to the ground (head injury)

Falls

- 1 storey = 12 feet = 3.6 m
- distance of fall: 50% mortality at 4 stories and 95% mortality at 7 stories
- position in which patient landed and type of surface
- assess for shock, lower extremity, spine and pelvic fractures

Gunshot Wounds (GSW)

- type of gun
 - handgun injuries: low or medium velocity, extent of injury may be limited to a small area
 - hunting and rifle injuries: high velocity, widespread injury
 - shot gun: widespread tissue destruction
- type of ammunition (e.g. hollow point bullets)
- range of shot
 - close range: massive tissue destruction, deposition of wadding into wound
- characterize route of entry, even or odd number of wounds and site of exit wound (if any)
 - GSW with hypotension: immediate transport to OR
 - hypotension indicates severe blood loss (>2 L blood loss in 70 kg patient is required to produce hypotension)

Stab Wounds

- route/direction of entry, length of blade
- type of penetration (stab, slash, impalement)
- victim recollection and witness reports are often inaccurate and may not correlate with depth/severity of wound
- if blade in-situ, DO NOT REMOVE – it may be tamponading bleeding vessel (to be removed in OR)



Vehicle vs. Pedestrian Crash
In adults look for triad of injuries (Waddle's triad):
1. Tibia-fibula or femur fracture
2. Truncal injury
3. Craniofacial injury



Cardiac box: sternal notch, nipples and xiphoid process; injuries inside this area should increase suspicion of cardiac injury.



Always completely expose and count the number of wounds.

Head Trauma

- see Neurosurgery, NS29
- 60% of trauma admissions have head injuries
- 60% of MVC-related deaths are due to head injury

Specific Injuries

- **fractures** (diagnosed by CT head, often not visible on x-ray)
 - A. skull fractures
 - vault fractures
 - ♦ linear, non-depressed
 - most common
 - typically occur over temporal bone, in area of middle meningeal artery (commonest cause of epidural hematoma)
 - ♦ depressed
 - open (associated overlying scalp laceration, torn dura) vs. closed
 - basal skull
 - ♦ typically occur through floor of anterior cranial fossa (longitudinal more common than transverse)
 - ♦ clinical diagnosis superior as poorly visualized on CT (Battle's sign, raccoon eyes, CSF rhinorrhea/otorrhea, hemotympanum)



Signs of Basal Skull Fracture
Battle's sign (bruised mastoid process)
Hemotympanum
Raccoon eyes (periorbital bruising)
CSF Rhinorrhea/Otorrhea

**Warning Signs of Severe Head Injury**

- GCS <8
- Deteriorating GCS
- Unequal pupils
- Lateralizing signs
- N.B.** Altered LOC is a hallmark of brain injury.

B. facial fractures (see Plastic Surgery, PL26)

- neuronal injury
 - beware of open fracture or sinus fractures (risk of infection)
 - unstable or displaced fractures (need semi-urgent plastics referral)
 - severe facial fractures may pose risk to airway from profuse bleeding

- **neuronal injury**

A. diffuse

- concussion
 - ♦ mild: temporary disturbance of neurological function, complete recovery
 - ♦ classical: temporary, reversible neurological disturbance, with temporary (<6 hrs) loss of consciousness, complete recovery
- diffuse axonal injury
 - ♦ mild: coma 6-24 hrs, possibly lasting deficit
 - ♦ moderate: coma >24hrs, little or no signs of brainstem dysfunction
 - ♦ severe: coma >24hrs, frequent signs of brainstem dysfunction

B. focal injuries

- contusions
- intracranial hemorrhage (epidural, subdural, intracerebral)

ASSESSMENT OF BRAIN INJURY

History

- pre-hospital status
- mechanism of injury

Physical Examination

- assume C-spine injury until ruled out
- vital signs
 - shock (not likely due to isolated brain injury, except in infants)
 - Cushing's response to increasing ICP (bradycardia, hypertension, irregular respirations)
- severity of injury determined by
 1. level of consciousness (LOC)
 - ♦ GCS ≤8 intubate, any change in score of 3 or more = serious injury
 2. pupils: size, anisocoria >1 mm (in patient with altered LOC), response to light
 3. lateralizing signs (motor/sensory)
 - ♦ may become more subtle with increasing severity of injury
- re-assess frequently

Investigations

- labs: CBC, electrolytes, coags, glucose, tox screen
- CT scan (non-contrast) to exclude intracranial mass lesions
- C-spine imaging, often with CT head and neck to exclude intracranial mass lesions

Management

- general
 - ABCs
 - ensure oxygen delivery to brain through intubation and prevent hypercarbia
 - maintain BP
 - treat other injuries, must treat hypotension, hypoxia (both contribute significantly to mortality)
- early neurosurgical consultation for acute and subsequent patient management
 - medical
 - ♦ seizure treatment/prophylaxis
 - benzodiazepines, phenytoin, phenobarbital
 - steroids are of no proven value
 - ♦ treat suspected raised ICP → consider if head injury with signs of increased ICP:
 - raise head of stretcher 20° if patient hemodynamically stable
 - intubate and hyperventilate (100% O₂) to a pCO₂ of 30-35 mmHg
 - mannitol 1g/kg infused as rapidly as possible
 - consider paralyzing meds if agitated/high airway pressures
 - maintenance of cerebral perfusion pressure is critical
 - surgical

Disposition

- neurosurgical ICU admission for severe head injuries (HI)
- in hemodynamically unstable patient with other injuries, prioritize most life-threatening injuries and maintain cerebral perfusion
- for minor head injury not requiring admission, provide 24-hour HI protocol to competent caregiver, follow-up with neurology as even seemingly minor HI may cause lasting deficits

Canadian CT Head Rule

The Lancet 2001; 357:9266;1391-1396

CT Head is only required for patients with minor head injuries with any one of the following:

High risk (for neurological intervention)

- GCS score <15 at 2 h after injury
- Suspected open or depressed skull fracture
- Any sign of basal skull fracture (hemotympanum, "raccoon" eyes, cerebrospinal fluid otorrhea/rhinorrhea, Battle's sign)
- Vomiting ≥2 episodes
- Age ≥65 years

Medium risk (for brain injury on CT)

- Amnesia after impact >30 min
- Dangerous mechanism (pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from height >3 feet or five stairs)

Minor head injury is defined as witnessed loss of consciousness, definite amnesia, or witnessed disorientation in a patient with a GCS score of 13-15.



Treatment of Increased ICP

- Elevate head of bed
- Mannitol
- Hyperventilate
- Paralyzing agents/sedating agents

See also Neurosurgery, NS6

Spine and Spinal Cord Trauma

- assume cord injury with significant falls (>12 ft), deceleration injuries, blunt trauma to head, neck or back
- spinal immobilization (cervical collar, spine board during patient transport only) must be maintained until spinal injury has been ruled out (Figure 2)
- vertebral injuries may be present without spinal cord injury; normal neurologic exam does not exclude spinal injury
- cord may be injured despite normal C-spine x-ray (SCIWARA = spinal cord injury without radiologic abnormality)
- injuries can include: complete/incomplete transection, cord edema, spinal shock

History

- mechanism of injury, previous deficits, SAMPLE
- neck pain, paralysis/weakness, paresthesia

Physical Exam

- ABCs
- abdo: ecchymosis, tenderness
- neuro: complete exam, including mental status
- spine: maintain neutral position, palpate C-spine for tenderness, step-off; log-roll, then palpate thoracic and lumbar spine; assess rectal tone
- extremities: check cap refill, suspect thoracolumbar injury with calcaneal fractures

Investigations

- labs: CBC, electrolytes, creatinine, glucose, coags, cross and type, tox screen
- imaging
 - full C-spine x-ray series for trauma (AP, lateral, odontoid)
- thoracolumbar x-rays
 - AP and lateral views
 - indications:
 - ♦ patients with C-spine injury
 - ♦ unconscious patients (with appropriate mechanism of injury)
 - ♦ patients with neurological symptoms or findings
 - ♦ patients with deformities that are palpable when patient log-rolled
 - ♦ patients with back pain
 - ♦ patients with bilateral calcaneal fractures (due to fall from height)
 - concurrent burst fractures of the lumbar or thoracic spine in 10% (T11-L2)
 - consider CT (for subtle bony injuries), MRI (for soft tissue injuries) if appropriate



Collar Everyone with at Least One of the Following Criteria

- Midline tenderness
- Neurological symptoms or signs
- Significant distracting injuries
- Head injury
- Intoxication
- Dangerous mechanism
- History of altered LOC



Note: Patients with penetrating trauma (especially gunshot and knife wounds) can also have spinal cord injury.



Of the investigations, the lateral C-spine x-ray is the single most important film. 95% of radiologically visible abnormalities are found on this film.



Cauda Equina Syndrome can occur with any spinal cord injury below T10 vertebrae. Look for incontinence, anterior thigh pain, quadriceps weakness, abnormal sacral sensation, decreased rectal tone and variable reflexes.

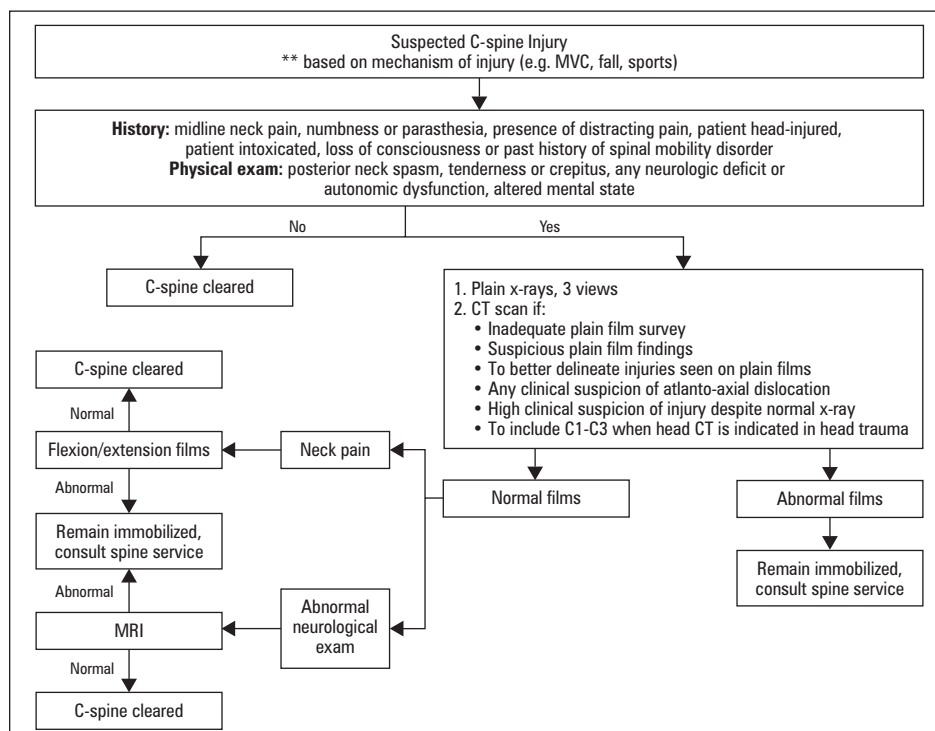


Figure 2. Approach to Clearing the C-spine

The Canadian C-spine Rule versus the NEXUS Low-risk Criteria in Patients with Trauma

NEJM 2003; 349(26):2510-8.

Purpose: To compare the clinical performance of the Canadian C-Spine Rule (CCR) and the National Emergency X-Radiography Utilization Study (NEXUS) Low-Risk Criteria (NLC).

Study: Trauma patients (n=8283) in stable condition were prospectively evaluated by both the CCR and NLC by 394 physicians before radiography. 2% of these patients had a C-spine injury.

Results: Compared to the NLC, the CCR was more sensitive (99.4 vs. 90.7%) and more specific (45.1 vs. 36.8%) after exclusion of indeterminate cases. The number of missed patients would be 1 for the CCR and 16 for the NLC. The range of motion was not evaluated in some CCR cases likely because physicians were not comfortable with the procedure and this may slightly lower the sensitivity or specificity of the CCR in practice.

Summary: The CCR is superior to the NLC in alert and stable patients with trauma. The use of the CCR can result in lower radiography rates.

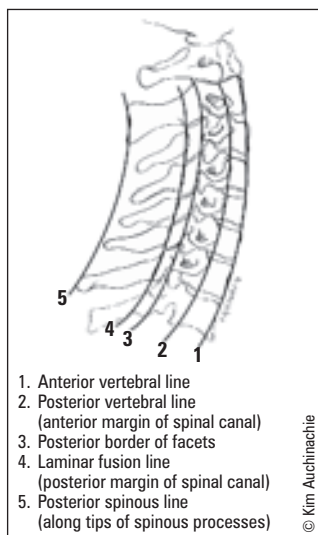
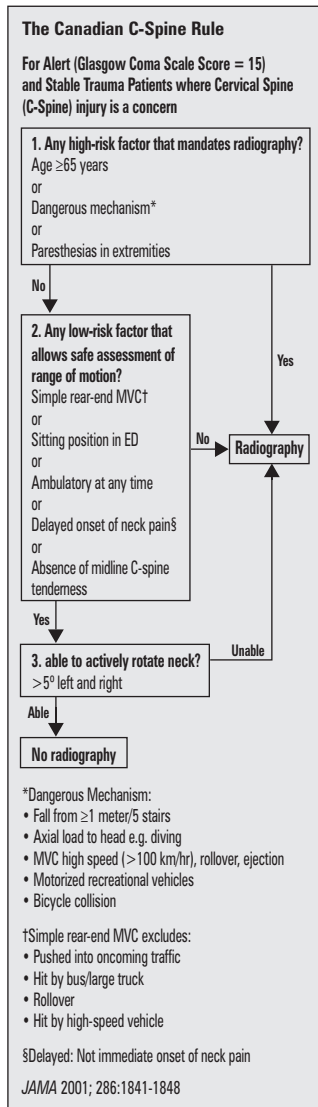


Figure 3. Lines of Contour on a Lateral C-Spine X-Ray

Can Clear C-spine if:

- no posterior midline cervical tenderness
- no evidence of intoxication
- oriented to person, place, time and event
- no focal neurological deficits
- no painful distracting injuries (e.g. long bone #)

Management of Cord Injury

- immobilize
- evaluate ABCs
- treat shock (maintain sBP >100 mmHg)
- insert NG and Foley catheter
- high dose steroids: methylprednisolone 30 mg/kg bolus, then 5.4 mg/kg/hr drip, start within 6-8 hrs of injury (controversial and recently has less support)
- complete imaging of spine and consult spine service if available
- continually reassess high cord injuries as edema can travel up cord
- if cervical cord lesion, watch for respiratory insufficiency
 - low cervical transection (C5-T1) produces abdominal breathing (phrenic innervation of diaphragm still intact)
 - high cervical cord injury (above C4) may require intubation and ventilation
- beware of hypotension (neurogenic shock)
 - treatment: warm blanket, Trendelenberg position (occasionally), volume infusion, consider vasopressors

Approach to C-Spine X-Rays

- 3-view C-spine series is the screening modality of choice
 1. lateral C1-T1 \pm swimmer's view (Figure 3, see Table 5 for interpretation)
 - ♦ lateral view is best, identifies 90-95% of injuries
 2. odontoid view (open mouth or oblique submental view) (see Figure 4)
 - ♦ examine the dens for fractures
 - beware of artifact (horizontal or vertical) caused by the radiological shadow of the teeth overlying the dens
 - if unable to rule out fracture, repeat view or consider CT or plain film tomography
 - ♦ examine lateral aspects of C1 and spacing relative to C2
 3. AP view
 - ♦ alignment of spinous processes in the midline
 - ♦ spacing of spinous processes should be equal
 - ♦ check vertebral bodies and facet dislocations

Supine Oblique Views

- rarely used
- better visualization of posterior element fractures (lamina, pedicle, facet joint)
- good to assess patency of neural foramina
- can be used to visualize the C7-T1 junction

Table 5. Interpretation of Lateral View: The ABCS

A Adequacy and Alignment	<ul style="list-style-type: none"> • Must see C1 to C7-T1 junction; if not, downward traction of shoulders, swimmer's view, bilateral supine obliques, or CT scan needed • Lines of contour – in children <8 years of age: can see physiologic subluxation of C2 on C3, and C3 on C4, but the spinolaminar line is maintained • Fanning of spinous processes – suggests posterior ligamentous disruption • Widening of facet joints • Check atlanto-occipital joint: <ul style="list-style-type: none"> ▪ Line extending inferiorly from clivus should transect odontoid ▪ Atlanto-axial articulation – widening of predental space (normal: <3 mm in adults, <5 mm in children) indicates injury of C1 or C2
B Bones	<ul style="list-style-type: none"> • Height, width and shape of each vertebral body • Pedicles, facets, and laminae should appear as one – doubling suggests rotation
C Cartilage	<ul style="list-style-type: none"> • Intervertebral disc spaces – wedging anteriorly or posteriorly suggests vertebral compression
S Soft Tissues	<ul style="list-style-type: none"> • Widening of retropharyngeal (normal: <7 mm at C1-4, may be wide in children <2 yrs on expiration) or retrotracheal spaces (normal: <22 mm at C6-T1, <14 mm in children <5 yrs)

Sequelae of C-spine Fractures

- decreased descending sympathetic tone (neurogenic/spinal shock) responsible for most sequelae
- autonomic dysreflexia: in patients with spinal cord injuries at or above the T6 level
 - common signs and symptoms: pounding headache, nasal congestion, feeling of apprehension or anxiety, visual changes, and marked increase in systolic and diastolic blood pressure
 - common triggers
 - ♦ urinary system: bladder distention, urinary tract infection, and kidney stones
 - ♦ GI causes: fecal impaction or bowel distention
- treatment: monitoring and controlling blood pressure, prior to addressing causative issue
- cardiac
 - no autoregulation, falling BP, decreasing HR, vasodilation
 - management: give IV fluids ± vasopressors
- respiratory
 - no cough reflex (risk of aspiration pneumonia)
 - no intercostal muscles ± diaphragm movement
 - management: intubate and maintain vital capacity
- gastrointestinal
 - ileus, vasodilation, bile and pancreatic secretion continues (>1L/day): risk of aspiration, GI stress ulcers
 - management: NG tube may be required for suctioning, feeding, etc.
- renal
 - hypoperfusion → give IV fluids
 - kidney still producing urine (bladder can rupture if patient not urinating)
 - management: Foley catheter may be required (measure urine output)
- skin
 - vasodilation, heat loss, no thermoregulation, atrophy (risk of skin ulcers)
- muscle
 - flaccidity, atrophy, decreased venous return
- penis
 - priapism

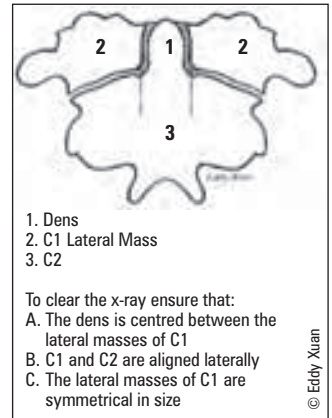


Figure 4. C-Spine X-Ray; Odontoid View



Prevertebral soft tissue swelling is only 49% sensitive for injury.



20% of C-spine fractures are accompanied by other spinal fractures, so ensure thoracic and lumbar spine x-rays are normal before proceeding to OR.



Trauma to the chest accounts for 50% of trauma deaths.



80% of all chest injuries can be managed non-surgically with simple measures such as intubation, chest tubes, and pain control.



3-way Seal for Open Pneumothorax (i.e. sucking chest wound)
Allows air to escape during the expiratory phase (so that you don't get a tension pneumothorax) but seals itself to allow adequate breaths during the inspiratory phase.

Chest Trauma

- two types
 - A. found and managed in 1° survey
 - B. found and managed in 2° survey

A. Life-Threatening Chest Injuries Found in 1° Survey (see Table 6)

Table 6. Life-Threatening Chest Injuries Found in 1° Survey

	Physical Exam	Investigations	Management
Airway Obstruction	<ul style="list-style-type: none"> • Anxiety, stridor, hoarseness, altered mental status • Apnea, cyanosis 	<ul style="list-style-type: none"> • Do not wait for ABG to intubate 	<ul style="list-style-type: none"> • Definitive airway management • Intubate early • Remove FB if visible with laryngoscope prior to intubation
Tension Pneumothorax	<ul style="list-style-type: none"> • Clinical diagnosis • One-way valve causing accumulation of air in pleural space 	<ul style="list-style-type: none"> • Non-radiographic diagnosis 	<ul style="list-style-type: none"> • Needle thoracostomy – large bore needle, 2nd ICS mid clavicular line, followed by chest tube in 5th ICS, anterior axillary line
Open Pneumothorax	<ul style="list-style-type: none"> • Gunshot or other wound (hole > 2/3 tracheal diameter) ± exit wound • Unequal breath sounds 	<ul style="list-style-type: none"> • ABG: decreased pO₂ 	<ul style="list-style-type: none"> • Air-tight dressing sealed on 3 sides • Chest tube • Surgery
Massive Hemothorax	<ul style="list-style-type: none"> • >1500 cc blood loss in chest cavity 	<ul style="list-style-type: none"> • Usually only able to do supine CXR – entire lung appears radioopaque as blood spreads out over posterior thoracic cavity 	<ul style="list-style-type: none"> • Restore blood volume • Chest tube • Thoracotomy if: <ul style="list-style-type: none"> ▪ >1500 cc total blood loss ▪ ≥200 cc/hr continued drainage

**DDx of Life Threatening Chest Injuries****HOT and FAT CHEST**

Hemothorax*
Open pneumothorax
Tension pneumothorax*

Flail chest
Airway obstruction
Tamponade*

Contusion: pulmonary, myocardial
Hernia: traumatic, diaphragmatic
ESophageal perforation
Tracheobronchial disruption/
Traumatic injury/Thoracic Aorta
Rupture*

*Rapidly Life Threatening

**Kussmaul's Sign Causes:**

Constrictive pericarditis
Right ventricular myocardial infarction
Tricuspid stenosis
Cardiac Tamponade



Ruptured diaphragm is more often diagnosed on the left side, as liver conceals right side defect.

**Aortic Tear: ABC WHITE**

X-ray features of Aortic tear
depressed left mainstem Bronchus
pleural Cap
Wide mediastinum (most consistent)
Hemothorax
Indistinct aortic knuckle
Tracheal deviation to right side
Esophagus (NG tube) deviated to right
(Note: present in 85% of cases, but cannot rule out)

**If Penetrating Neck Trauma present, DON'T:**

- Clamp structures (can damage nerves)
- Probe
- Insert NG tube (leads to bleeding)
- Remove weapon/impaled object

Table 6. Life-Threatening Chest Injuries Found in 1° Survey (continued)

	Physical Exam	Investigations	Management
Flail Chest <ul style="list-style-type: none">• Free-floating segment of chest wall due to >2 rib fractures, each at 2 sites• Underlying lung contusion (cause of morbidity and mortality)	<ul style="list-style-type: none">• Paradoxical movement of flail segment• Palpable crepitus of ribs• Decreased air entry on affected side	<ul style="list-style-type: none">• ABG: decreased pO₂, increased pCO₂• CXR: rib fractures, lung contusion	<ul style="list-style-type: none">• O₂ + fluid therapy + pain control• Judicious fluid therapy in absence of systemic hypotension• Positive pressure ventilation• ± intubation and ventilation
Cardiac Tamponade <ul style="list-style-type: none">• Clinical diagnosis• Pericardial fluid accumulation impairing ventricular function	<ul style="list-style-type: none">• Penetrating wound (usually)• Beck's triad: hypotension, distended neck veins, muffled heart sounds• Tachycardia, tachypnea• Pulsus paradoxus• Kussmaul's sign	<ul style="list-style-type: none">• Echocardiogram• Bedside ultrasound (FAST)	<ul style="list-style-type: none">• IV fluids• Pericardiocentesis• Open thoracotomy

B. Potentially Life-Threatening Chest Injuries Found in 2° Survey (see Table 7)

- need to have high index of suspicion, usually dependent on mechanism of injury

Table 7. Potentially Life-Threatening Chest Injuries Found in 2° Survey

	Physical Exam	Investigations	Management
Pulmonary Contusion	<ul style="list-style-type: none"> • Blunt trauma to chest • Interstitial edema impairs compliance and gas exchange 	<ul style="list-style-type: none"> • CXR: areas of opacification of lung within 6 hours of trauma 	<ul style="list-style-type: none"> • Maintain adequate ventilation • Monitor with ABG, pulse oximeter and ECG • Chest physiotherapy • Positive pressure ventilation if severe
Ruptured Diaphragm	<ul style="list-style-type: none"> • Blunt trauma to chest or abdomen (e.g. high lap belt in MVC) 	<ul style="list-style-type: none"> • CXR: abnormality of diaphragm/lower lung fields/NG tube placement • CT scan and endoscopy – sometimes helpful for diagnosis 	<ul style="list-style-type: none"> • Laparotomy for diaphragm repair and because of associated intra-abdominal injuries
Esophageal Injury	<ul style="list-style-type: none"> • Usually penetrating trauma (pain out of proportion to degree of injury) 	<ul style="list-style-type: none"> • CXR: mediastinal air (not always) • Esophagram (Gastrografin) • Flexible esophagoscopy 	<ul style="list-style-type: none"> • Early repair (within 24 hrs) improves outcome but all require repair
Aortic Tear	<ul style="list-style-type: none"> • Sudden high speed deceleration (e.g. MVC, fall, airplane crash), complaints of chest pain, dyspnea, hoarseness (frequently absent) • Decreased femoral pulses, differential arm BP (arch tear) 	<ul style="list-style-type: none"> • CXR, CT scan, transesophageal echo (TEE), aortography (gold standard) • See sidebar for CXR features 	<ul style="list-style-type: none"> • Thoracotomy (may treat other severe injuries first)
Blunt Myocardial Injury (rare)	<ul style="list-style-type: none"> • Blunt trauma to chest (usually in setting of multi-system trauma and therefore difficult to diagnose) • Physical examination: overlying injury, e.g. fractures, chest wall contusion 	<ul style="list-style-type: none"> • ECG: arrhythmias, ST changes • Patients with a normal ECG and normal hemodynamics never get dysrhythmias 	<ul style="list-style-type: none"> • O₂ • Antiarrhythmic agents • Analgesia

C. Other Potentially Life-Threatening Injuries Related to the Chest**Penetrating Neck Trauma**

- includes all penetrating trauma to the three zones of the neck (Figure 5)
- management: injuries deep to platysma require further evaluation by angiography, contrast CT or surgery
- do not explore penetrating neck wounds except in the OR

Airway Injuries

- always maintain a high index of suspicion
- larynx
 - history: strangulation, clothes line, direct blow, blunt trauma, any penetrating injury involving platysma
 - triad: hoarseness, subcutaneous emphysema, palpable fracture crepitus
 - other symptoms: hemoptysis, dyspnea, dysphonia
 - investigations: CXR, CT scan, arteriography (if penetrating)
 - management
 - ♦ airway – manage early because of edema
 - ♦ C-spine may also be injured, consider mechanism of injury
 - ♦ surgical – tracheotomy vs. repair
- trachea/bronchus
 - frequently missed
 - history: deceleration, penetration, increased intra-thoracic pressure; complaints of dyspnea, hemoptysis
 - examination: subcutaneous air, Hamman's sign (crunching sound synchronous with heart beat)
 - CXR: mediastinal air, persistent pneumothorax or persistent air leak after chest tube inserted for pneumothorax
 - management: surgical repair if >1/3 circumference

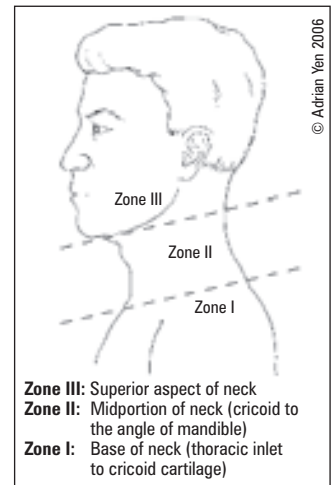


Figure 5. Zones of the Neck in Trauma

Abdominal Trauma

- two mechanisms
 - blunt: usually causes solid organ injury (spleen injury is most common)
 - penetrating: usually causes hollow organ injury or liver injury (most common)

BLUNT TRAUMA

- results in two types of hemorrhage
 - intra-abdominal bleed
 - retroperitoneal bleed
- adopt high clinical suspicion of bleeding in multi-system trauma

History

- mechanism of injury, SAMPLE history

Physical Exam

- often unreliable in multi-system trauma
 - slow blood loss not immediately apparent
 - other injuries may mask symptoms
 - serial examinations are required
- abdomen
 - inspect: contusions, abrasions, seatbelt sign, distention
 - auscultate: bruits, bowel sounds
 - palpate: tenderness, rebound tenderness, rigidity, guarding
 - DRE: rectal tone, blood, bone fragments, prostate location
 - placement of NG, foley catheter should be considered part of the abdo exam
- other systems to assess: CVS, respiratory (possibility of diaphragm rupture), pelvis, back, neuro as it pertains to abdo sensation, GU

Investigations

- labs: CBC, electrolytes, coags, cross & type, glucose, creatinine, CK, lipase, amylase, liver enzymes, ABG, blood EtOH, β -hCG, U/A, tox screen
- imaging: see Table 8

Table 8. Imaging in Abdominal Trauma

Imaging	Strengths	Limitations
X-Ray	Chest (looking for free air under diaphragm, diaphragmatic hernia, air-fluid levels), pelvis, cervical, thoracic, lumbar spines	Soft tissue not well visualized
CT scan	Most specific test	Radiation exposure 20x more than x-ray Cannot use if hemodynamic instability
Diagnostic Peritoneal Lavage (DPL)	Most sensitive test Tests for intra-peritoneal bleed	Cannot test for retroperitoneal bleed or diaphragmatic rupture Cannot distinguish lethal from trivial bleed Results can take up to 1 hr
Ultrasound: FAST (Focused Abdominal Sonogram for Trauma)	Identifies presence/absence of free fluid in peritoneal cavity RAPID exam: less than 5 minutes Can also examine pericardium and pleural cavities	NOT used to identify specific organ injuries If patient has ascites, FAST will be falsely positive



Seatbelt Injuries may Cause

- Retroperitoneal duodenal trauma
- Intraperitoneal bowel transection
- Mesenteric injury
- L-spine injury



Indications for Foley and NG Tube in Abdominal Trauma

Foley catheter: unconscious or patient with multiple injuries who cannot void spontaneously.

Contraindications: blood at the meatus, an ecchymotic scrotum, or a "high-riding" prostate on DRE (retrograde cystourethrogram is indicated to rule out a urethral tear or ruptured bladder).

NG tube: used to decompress the stomach and proximal small bowel.

Contraindications: facial fractures or basal skull fractures suspected.



Criteria for Positive Lavage

- >10 cc gross blood
- Bile, bacteria, foreign material
- RBC count > 100,000 x 10⁶/L
- WBC > 500 x 10⁶/L, amylase > 175 IU


Laparotomy is Mandatory if Penetrating Trauma and:

- Shock
- Peritonitis
- Evisceration
- Free air in abdomen
- Blood in NG tube, Foley catheter, or on rectal exam


"Rule of Thirds" for stab wounds:

- 1/3 do not penetrate peritoneal cavity
- 1/3 penetrate but are harmless
- 1/3 cause injury requiring surgery



Gross hematuria suggests bladder injury.



In the case of gross hematuria, the GU system is investigated from distal to proximal (i.e. urethrogram, cystogram, etc.)

- imaging must be done if
 - equivocal abdominal examination, suspected intra-abdominal injury or distracting injuries
 - multiple trauma patient resulting in unreliable physical exam (altered sensorium, e.g. secondary to drugs, alcohol, head trauma, or distracting injury; spinal cord injury resulting in abdominal anesthesia)
 - unexplained shock/hypotension
 - multiple trauma patients who must undergo general anesthesia for orthopaedic, neurosurgical, or other injuries
 - fractures of lower ribs, pelvis, spine
 - positive FAST

Management

- general: ABCs, fluid resuscitation and stabilization
- surgical: watchful wait vs. laparotomy
- solid organ injuries: decision based on hemodynamic stability, not the specific injuries
- hemodynamically unstable or persistently high transfusion requirements: laparotomy
- hollow organ injuries: laparotomy
- even if low suspicion on injury: admit and observe for 24 hours

PENETRATING TRAUMA

- high risk of gastrointestinal perforation and sepsis
- history: size of blade, calibre/distance from gun, route of entry
- local wound exploration under direct vision may determine lack of peritoneal penetration (not reliable in inexperienced hands) with the following exceptions:
 - thoracoabdominal region (may cause pneumothorax)
 - back or flanks (muscles too thick)

Management

- general: ABCs, fluid resuscitation and stabilization
- gunshot wounds → always require laparotomy

Genitourinary Tract Injuries

- see Urology, U32

Etiology

- blunt trauma – often associated with pelvic fractures
 - renal contusions (minor injury – parenchymal ecchymoses with intact renal capsule)
 - renal parenchymal tears/laceration: non-communicating (hematoma) vs. communicating (urine extravasation, hematuria)
 - extraperitoneal rupture of bladder from pelvic fracture fragments
 - intraperitoneal rupture of bladder from trauma and full bladder
 - anterior (bulbous) urethral damage with pelvic fractures
 - ureter: rare, at uretero-pelvic junction
- penetrating trauma
 - damage to: kidney, bladder, ureter (rare)
- acceleration/deceleration injury
 - renal pedicle injury – high mortality rate (laceration and thrombosis of renal artery, renal vein, and their branches)
- iatrogenic
 - ureter (from instrumentation)

History

- mechanism of injury
- hematuria (microscopic or gross), blood on underwear
- dysuria, urinary retention
- history of hypotension

Physical Examination

- abdominal pain, flank pain, costovertebral angle (CVA) tenderness, upper quadrant mass, perineal lacerations
- DRE: sphincter tone, position of prostate, presence of blood
- scrotum: ecchymoses, lacerations, testicular disruption, hematomas
- bimanual exam, speculum exam
- extraperitoneal bladder rupture: pelvic instability, suprapubic tenderness from mass of urine or extravasated blood
- intraperitoneal bladder rupture: acute abdomen

Investigations

- urethra: retrograde urethrography
- bladder: urinalysis, CT scan, urethrogram, \pm retrograde cystoscopy, \pm cystogram (distended bladder + post-void)
- ureter: retrograde ureterogram
- renal: CT scan (best, if hemodynamically stable), intravenous pyelogram (IVP)

Management

- urology consult
- renal
 - minor injuries – conservative management
 - ♦ bedrest, hydration, analgesia, antibiotics
 - major injuries – admit
 - ♦ conservative management with frequent reassessments, serial urinalysis, \pm reimaging
 - ♦ surgical repair (exploration, nephrectomy): e.g. hemodynamically unstable or continuing to bleed >48 h, major urine extravasation, renal pedicle injury, all penetrating wounds and major lacerations, infections, renal artery thrombosis
- ureter
 - uretero-uretostomy
- bladder
 - extraperitoneal
 - ♦ minor rupture: Foley drainage x 10-14 days
 - ♦ major rupture: surgical repair
 - intraperitoneal
 - ♦ drain abdomen and surgical repair
- urethra
 - anterior: conservative, if cannot void \rightarrow Foley or suprapubic cystostomy and antibiotics
 - posterior: suprapubic cystostomy (avoid catheterization) \pm surgical repair

Orthopaedic Injuries

- see [Orthopaedics](#) (*Shoulder, Knee, Wrist, Ankle*)

Goals of ED Treatment

- identify injuries accurately and address potentially life/limb threatening problems appropriately
- reduce and immobilize fractures (cast/splint) as appropriate
- provide adequate pain relief
- arrange proper follow-up if necessary

History

- use SAMPLE
- mechanism of injury may be very important

Physical Examination

- **Look** (inspection): “SEADS” Swelling, Erythema, Atrophy, Deformity, Skin changes (e.g. bruises)
- **Feel** (palpation): all joints/bones – local tenderness, swelling, warmth, crepitus, joint effusions, subtle deformity
- **Move**: joints affected plus above and below injury – active ROM preferred to passive
- **Neurovascular status**: distal to injury (BEFORE and AFTER reduction)

LIFE AND LIMB THREATENING INJURIES (see Table 9)

- threat to life is usually due to blood loss (e.g. up to 3 L in pelvic fractures, 1.5 L per long bone fracture)
- threat to limb is usually due to interruption of blood supply to distal part of limb or to susceptible part of bone

Table 9. Life and Limb Threatening Orthopedic Injuries

Life Threatening Injuries	Limb Threatening Injuries
Major pelvic fractures	Fracture/dislocation of ankle (talar AVN)
Traumatic amputations	Crush injuries
Massive long bone injuries (beware of fat emboli)	Compartment syndrome
Vascular injury proximal to knee/elbow	Open fractures
	Dislocations of knee/hip
	Fractures above knee/elbow



Description of Fractures

SOLARTAT

Site
Open vs. closed
Length
Articular
Rotation
Translation
Alignment/Angulation
Type (e.g. Salter-Harris, etc.)



Reasons for Emergent Orthopaedic Consultation

- Compartment syndrome
- Irreducible dislocation
- Circulatory compromise
- Open fracture
- Injury requiring surgical repair



When Dealing with an Open Fracture, Remember "STAND"

Splint
Tetanus prophylaxis
Antibiotic
Neurovascular status (before and after)
Dressings (to cover wound)



Vascular injury/compartament syndrome is suggested by "The 6 Ps":

Pulse discrepancies
Pallor
Paresthesia/hypoesthesia
Paralysis
Pain (especially when refractory to usual analgesics)
Polar (cold)

Open Fractures

- communication between fracture site and external surface of skin – risk of osteomyelitis
- remove gross debris, irrigate, cover with sterile dressing – formal irrigation and debridement often done in the OR
- control bleeding with pressure (no clamping)
- splint
- antibiotics (1st generation cephalosporin and aminoglycoside) and tetanus prophylaxis
- must secure definitive surgical care within 6-8 hours

Vascular Injuries

- realign limb/apply longitudinal traction and reassess pulses (e.g. Doppler probe)
- surgical consult
- direct pressure if external bleeding

Compartment Syndrome

- increased interstitial pressure in an anatomical "compartment" (forearm, calf) with little room for expansion, resulting in decreased perfusion and potential muscle/nerve necrosis
- **excessive** pain which is worse with passive stretching and refractory to analgesia is the hallmark sign early on; also look for "the 6 Ps" (see side bar)
- requires prompt decompression – remove constrictive casts, dressings; fasciotomy may be needed emergently

UPPER EXTREMITY INJURIES

- anterior shoulder dislocation
 - axillary nerve (lateral aspect of shoulder) and musculocutaneous nerve (extensor aspect of forearm) at risk
 - seen on lateral view: humeral head anterior to glenoid
 - ♦ reduce (traction, scapular manipulation), immobilize in internal rotation, repeat x-ray, out-patient follow-up with ortho
 - ♦ with forceful injury, look for fracture
- Colles' fracture (Figure 6)
 - distal radius fracture with dorsal displacement from Fall On an Outstretched Hand (FOOSH)
 - AP film: shortening, radial deviation, radial displacement
 - lateral film: dorsal displacement, volar angulation
 - reduce, immobilize with splint, out-patient follow-up with ortho or immediate orthopedic referral if complicated fracture
 - if involvement of articular surface, emergent orthopedic referral
- scaphoid fracture (see Figure 7 for review of carpal bones)
 - tenderness in anatomical snuff box, pain on scaphoid tubercle, pain on axial loading of thumb
 - negative x-ray: thumb spica splint, re-x-ray in 1 week ± bone scan
 - positive x-ray: thumb spica splint x 6-8 weeks, re-x-ray in 2 weeks
 - risk of avascular necrosis (AVN) of scaphoid if not immobilized
 - outpatient ortho follow-up

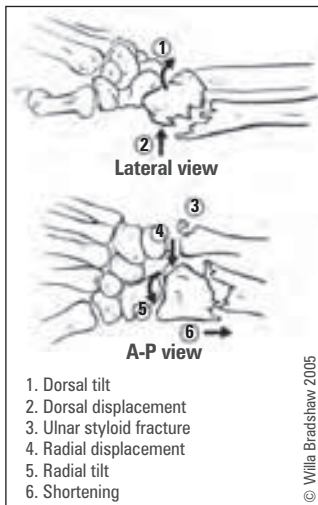


Figure 6. Colles' Fracture

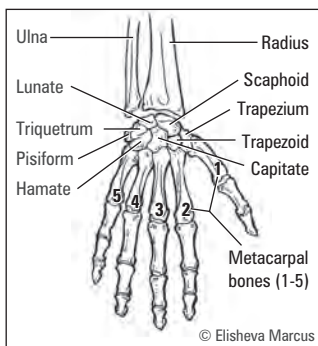
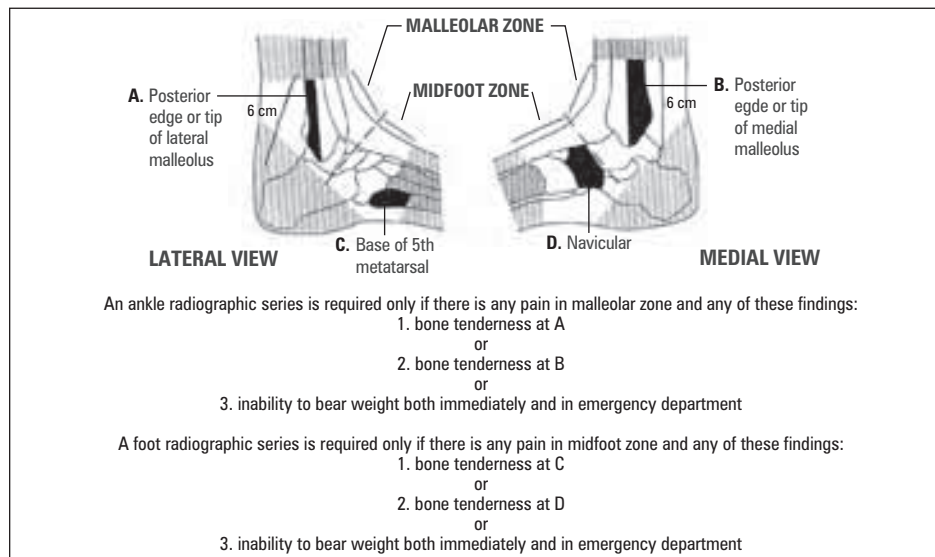


Figure 7. Carpal Bones

LOWER EXTREMITY INJURIES

- ankle and foot fractures
 - see Ottawa Ankle and Foot Rules (Figure 8)
- knee injuries
 - see Ottawa Knee Rules (Figure 9)
- avulsion of the base of 5th metatarsal
 - occurs with inversion injury
 - supportive tensor or below knee walking cast for 3 weeks
- calcaneal fracture
 - associated with fall from height
 - associated injuries may involve ankles, knees, hips, pelvis, lumbar spine



A knee x-ray examination is required only for acute injury patients with one or more of:

- Age 55 years or older
- Tenderness at head of fibula
- Isolated tenderness of patella*
- Inability to flex to 90°
- Inability to bear weight both immediately and in the emergency department (four steps)**

*no bony tenderness of knee other than patella

**unable to transfer weight twice onto each lower limb regardless of limping

Figure 9. Ottawa Knee Rules

Adapted from: Stiell et. al. *JAMA* 1997; 278:2075-2079

Wound Management

Goals of ED Treatment

- identify injuries and stop any active bleeding – direct pressure
- manage pain
- wound examination and exploration (history and physical)
- cleansing ± antibiotic and tetanus prophylaxis
- repair and dressing

Tetanus Prophylaxis

- both tetanus toxoid (Td) and immunoglobulin (TIG) are safe (and indicated) in pregnancy

Table 10. Guidelines for Tetanus Prophylaxis for Wounds

Immunization History	Non Tetanus Prone Wounds		Tetanus Prone Wounds ¹	
	Td ²	TIG ³	Td	TIG
Uncertain or <3 doses	Yes	No	Yes	Yes
3 or more, none for >10 years	Yes	No	Yes	No
3 or more, 5 to 10 years ago	No	No	Yes	No
3 or more, <4 years ago	No	No	Yes	No

¹ wounds >6 hours old, >1 cm deep, puncture wounds, avulsions, wounds resulting from missiles, crush wounds, burns, frostbite, wounds contaminated with dirt, feces, soil, or saliva

² 0.5 mL IM tetanus and diphtheria toxoids (Td), adsorbed

³ tetanus immune globulin (TIG), 250 units deep IM

Source: *MMWR* 2001; 50(20):418-427. *MMWR* 1991; 40(RR12):1-52.

Bruises

- non palpable = ecchymosis
- palpable collection (not swelling) = hematoma following blunt trauma
- assess for coagulopathy (e.g. liver disease), anticoagulant use



Reasons for Splinting

- Reduces pain
- Reduces further damage to vessels and nerves
- Reduces risk of inadvertently converting a closed fracture into an open fracture
- Facilitates patient transport

Accuracy of Ottawa Ankle Rules to Exclude Fractures of the Ankle and Mid-Foot: Systematic Review

BMJ 2003; 326(7386):417

This systematic review and meta-analysis of 27 studies including 15,581 patients evaluated the sensitivity and specificity of the Ottawa ankle rules for excluding fractures of the ankle and mid-foot.

Results: The pooled likelihood ratio of a negative result (obtaining a false negative) among those with a fracture was determined to be 0.08 for both the ankle and mid-foot.

Reviewers' Conclusions: The Ottawa ankle rules provide an accurate instrument for excluding fractures of the ankle and mid-foot with a sensitivity of almost 100% and a specificity of 26%. The use of this instrument can reduce the number of unnecessary radiographs.



Acute Treatment of Contusions

RICE

Rest
Ice
Compression
Elevation



Suture Use and Duration

Suture to	Close with nylon or other nonabsorbable suture	Approx. duration (days)
Face	6-0	5
Not Joint	4-0	7
Joint	3-0	10
Scalp	4-0	7
Mucous Membrane	absorbable (vicryl)	N/A

N.B. Patients on steroid therapy may need sutures in for longer periods of time



Alternatives to Sutures

- Tissue glue
- Steristrips®
- Staples



Where **NOT** to use local anesthetic with epinephrine:
Ears, Nose, Fingers, Toes and Nose (Penis)



Differential Diagnosis of Cellulitis
Necrotizing Fasciitis
Gas gangrene
Cutaneous anthrax
Vaccinia vaccination
Insect bite (hypersensitivity)
Acute gout
DVT
Fixed drug eruption
Kawasaki's
Pyoderma gangrenosum



Features of Necrotizing Fasciitis Infection

ABCDE

- A** – Anaerobic, Aerobic, Adult, Antibiotics refractory
- B** – Bacterial synergistic gangrene, Blood count higher than normal
- C** – Cellulitis, Crepitus, and Coagulopathy
- D** – Dermal gangrene, Delay in presentation almost fatal
- E** – Erythema with spreading Edema

Abrasions

- partial to full thickness break in skin
- management
 - clean thoroughly, ± local anesthetic, with brush to prevent foreign body impregnation (tattooing)
 - antiseptic ointment (Polysporin® or Vaseline®) for 7 days for facial and complex abrasions
 - tetanus prophylaxis (Table 10)

Lacerations

- see also Plastic Surgery, PL6
- consider every structure deep to a laceration injured until proven otherwise
- in hand injury patients, include following in history: handedness, occupation, mechanism of injury, previous history of injury
- physical exam
 - think about underlying anatomy
 - examine tendon function actively against resistance and neurovascular status distally
 - clean and explore under local anesthetic; look for partial tendon injuries
 - x-ray or ultrasound wounds if a foreign body is suspected (e.g. shattered glass) and not found when exploring wound (remember: not all foreign bodies are radiopaque), or if suspect intra-articular involvement
- management
 - disinfect skin/use sterile techniques
 - irrigate copiously with normal saline
 - analgesia ± anesthesia (Figure 10)
 - maximum dose of lidocaine:
 - ♦ 7 mg/kg with epinephrine
 - ♦ 5 mg/kg without epinephrine
- in children, topical anesthetics such as LET (lidocaine, epinephrine and tetracaine) and in selected cases a short-acting benzodiazepine (midazolam or other agents) for sedation and amnesia are useful
- secure hemostasis
- evacuate hematomas, debride non-viable tissue, remove hair and remove foreign bodies
- ± prophylactic antibiotics
- suture unless delayed presentation, a puncture wound, or mammalian bite
- take into account patient and wound factors when considering suturing
- advise patient when to have sutures removed

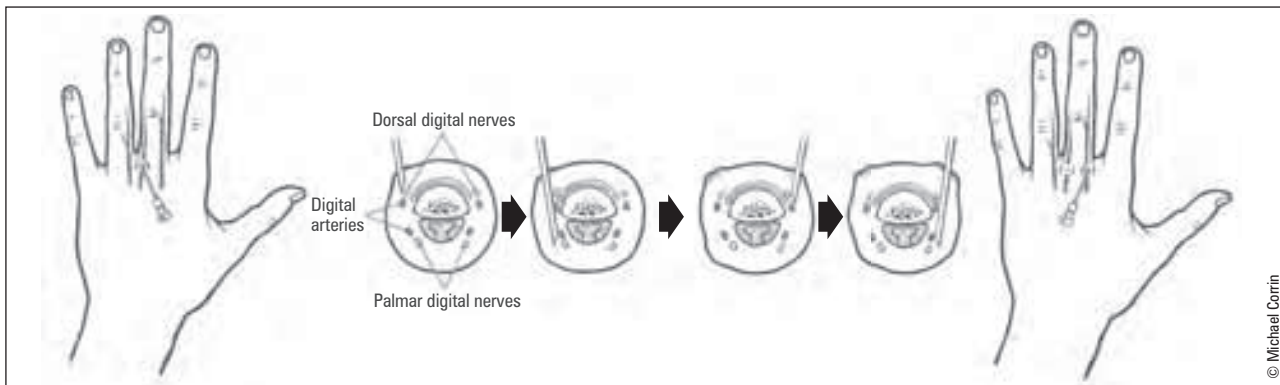


Figure 10. Digital Block – Local Anesthesia of Digits



Early wound irrigation and debridement are the most important factors in decreasing infection.

Cellulitis

- see also Plastic Surgery, PL12
- localized infection of the dermis
- bacterial (*S. aureus*, GAS, *H. influenzae*, occasionally *Pseudomonas* spp., MRSA) infection of skin and subcutaneous tissues
- look for “rubor, calor, dolor, tumour” (erythema, warmth, pain, swelling)
- have high index of suspicion in patients who are immunocompromised (e.g. HIV, DM), vasculopathies, IV drug users
- treat with immobilization and elevation of infected area, antibiotics, analgesics, and close follow-up
- antibiotics for mild cellulitis: PO cephalexin or cloxacillin
- if MRSA: PO clindamycin, doxycycline, TMP-SMX; IV vancomycin if bacteremic

Abscess

- may be associated with a retained foreign body
- look for warm, swollen, painful, erythematous fluctuant masses
- ensure absence of systemic symptoms and presence of subcutaneous air in simple abscesses
- anesthetize locally
- treat with incision and drainage ± antibiotics – apply warm compress, give analgesics



Which Abscesses Need Antibiotics?

- Evidence of systemic illness (e.g. cellulitis)
- Immunocompromised patient
- Patient at risk for endocarditis

Trauma in Pregnancy

- priorities: Airway, Breathing, Circulation

Hemodynamic Considerations

- near term, inferior vena caval compression in the supine position can decrease cardiac output by 30-40% (see *Maternal Physiology*, *Obstetrics*, OB3)
 - use left lateral decubitus (LLD) positioning or hip bolster to alleviate compression and increase blood return if BP is low
- BP drops 5-15 mmHg systolic in 2nd trimester, increases to normal by term
- HR increases 15-20 beats per minute by 3rd trimester

Blood Considerations

- physiologic macrocytic anemia of pregnancy (Hb 100-120)
- WBC increases to high of 20,000

Shock

- pregnant patients may lose 35% of blood volume without typical signs of shock (i.e. tachycardia, hypotension)
- the fetus may be in "shock" due to contraction of the uteroplacental circulation
- fetal HR changes are an early warning of maternal circulatory compromise

Management Differences

- place bolster under right hip to stop inferior vena cava compression
- fetal monitoring (continuous tocographic monitoring if possible viable fetus >20 weeks)
- early obstetrical consult
- do not avoid necessary x-rays, but shield as much as possible
- consider need for RhoGAM if mother Rh negative



The best treatment for the fetus is the effective treatment of the mother.

Approach to Common ER Presentations

Abdominal Pain

Rule Out Life-Threatening Causes

- CVS: MI, aortic dissection, ruptured AAA (tearing pain)
- GI: perforated viscus, hepatic/splenic injury, ischemic bowel (diffuse pain)
- gynecologic: ectopic pregnancy

Additional Differential Diagnosis

- GI: appendicitis, diverticulitis, bowel obstruction, hepatitis, cholecystitis, pancreatitis
- urinary: cystitis, pyelonephritis, ureteral calculi
- genital
 - female: pelvic inflammatory disease (PID)/salpingitis, tubo-ovarian abscess, ovarian torsion, ovarian cyst, endometriosis
 - male: testicular torsion, epididymitis
- other: diabetic ketoacidosis (DKA), Herpes Zoster Virus (HZV), intra-abdominal abscess, pneumonia, lead poisoning, porphyria, sickle cell crisis, psychiatric

History and Physical Examination

- determine onset, course, location and character of pain: PQRST
- broad differential, including GU, Gyne, GI, respiratory, and CV systems
- recent/remote abdominal trauma/surgeries
- general appearance, vitals, ABCs
- respiratory, CVS
- abdomen and back: CVA tenderness, ecchymoses, stigmata of liver disease, DRE, pelvic exam (females), genital exams (males)
- extremities: differential pulses, psoas/obturator sign

Investigations

- do not delay consultation if patient unstable
- CBC, electrolytes, glucose, LFTs, amylase, BUN/creat, U/A, + others if indicated: β -hCG, ECG, troponins
- AXR: look for calcifications, free air, gas pattern, air fluid levels
- CXR upright: look for pneumoperitoneum (free air under diaphragm)
- U/S: biliary tract, ectopic pregnancy, AAA, free fluid
- CT: trauma, AAA, pancreatitis, nephro/urolithiasis, appendicitis and diverticulitis



Red Flags

- Extremes of age
- Unstable vital signs
- Fever
- Signs/symptoms of shock
- Rapid onset severe pain



Abdominal Assessment in all 4 Quadrants

DR. GERM

Distention
Rigidity
Guarding
Evisceration/Ecchymosis
Rebound tenderness
Masses



If both AST and ALT elevated,
AST > ALT indicates potential alcohol
related hepatic diseases
ALT > AST indicates viral hepatic
pathology
If ALP and GGT elevated, think
biliary tree



Old age, pregnancy (T3), and chronic corticosteroid use can blunt peritoneal findings, so have increased suspicion of intrabdominal process in these individuals!



Unstable patients should not be sent for imaging.



All women of childbearing age assumed to be pregnant until proven otherwise.



Gynecological Causes of Pelvic Pain:

Ovarian Cyst
Dysmenorrhea
Mittelschmerz
Endometriosis
Ovarian Torsion
Uterine Fibroids/neoplasm
Adnexal Neoplasm
PID + Cervicitis



Ultrasound is the preferred imaging modality in the assessment of acute pelvic pain.

Management

- NPO, IV, NG tube, analgesics
 - growing evidence that small amounts of narcotic analgesics improve diagnostic accuracy of physical exam of surgical abdomen
- consult as necessary: general surgery, vascular, gynecology, etc.

Disposition

- admission: in addition to a surgical abdomen, admission is sometimes required for workup of abnormal findings on investigation, IV antibiotics, pain control, etc.
- discharge: patients with a negative lab and imaging workup who improve clinically during their stay; instruct the patient to return if severe pain, fever, or persistent vomiting develop

Acute Pelvic Pain

Etiology

- gynecological
 - 2nd most common gynecological complaint after vaginal bleeding
 - ruptured ovarian cysts – most common cause of pelvic pain, follicular cyst most common type
 - ovarian torsion – rare, 50% will have ovarian mass
 - leiomyomas (uterine fibroids) – especially with torsion of a pedunculated fibroid or in pregnant patient (degeneration)
 - ectopic pregnancy – ruptured/expanding/leaking
 - spontaneous abortion – threatened or incomplete
 - infection – PID, endometritis, tubo-ovarian abscess
 - dysmenorrhea and endometriosis
- non-gynecological
 - GI – appendicitis, constipation, bowel obstruction, gastroenteritis, diverticulitis, IBD, IBS
 - GU – cystitis, pyelonephritis, ureteric stone
 - other – porphyria, abdominal angina, aneurysm, hernia, zoster

History and Physical Exam

- determine onset, course, location and character of the pain
- associated symptoms: vaginal bleeding, bowel or bladder symptoms, radiation
- vitals
- gynecological exam
- abdominal exam

Investigations

- β -hCG for all women of childbearing age
- CBC and differential, PTT/INR
- pelvic and abdominal U/S – evaluate adnexa, look for free fluid in the pelvis or masses, evaluate thickness of endometrium
- doppler flow studies for ovarian torsion

Management

- general: analgesia, determine if admission and consults needed
 - gynecology consult if history and physical suggestive of serious cause
 - other consults as indicated – general surgery, urology, etc.
- specific:
 - ovarian cysts
 - ♦ unruptured or ruptured and hemodynamically stable – analgesia and follow-up
 - ♦ ruptured with significant hemoperitoneum – may require surgery
 - ovarian torsion – surgical detorsion or removal of ovary
 - uncomplicated leiomyomas, endometriosis and secondary dysmenorrhea can usually be treated on an outpatient basis, discharge with gynecology follow-up
 - PID: requires broad spectrum antibiotics

Disposition

- patients requiring IV therapy or surgery should be admitted
- patients to be discharged should be given clear instructions for appropriate follow-up

Altered Level of Consciousness (LOC)



Definitions

- altered mental status – collective, non-specific term referring to change in cognitive function, behaviour, or attentiveness
- delirium – acute, transient, fluctuating, potentially reversible organic brain disorder presenting as altered LOC and attentiveness (see [Psychiatry](#), PS17)
- dementia – insidious, progressive, organic brain disorder with change in memory, judgment, personality and cortical function (see [Psychiatry](#), PS18)
- lethargy – state of decreased awareness and alertness (patient may appear wakeful)
- stupor – unresponsiveness from which the patient can be aroused
- coma – a sleep-like state, not arousable to consciousness (Figure 11)
- use the GCS to evaluate LOC (see *Initial Patient Assessment and Management*, ER2)

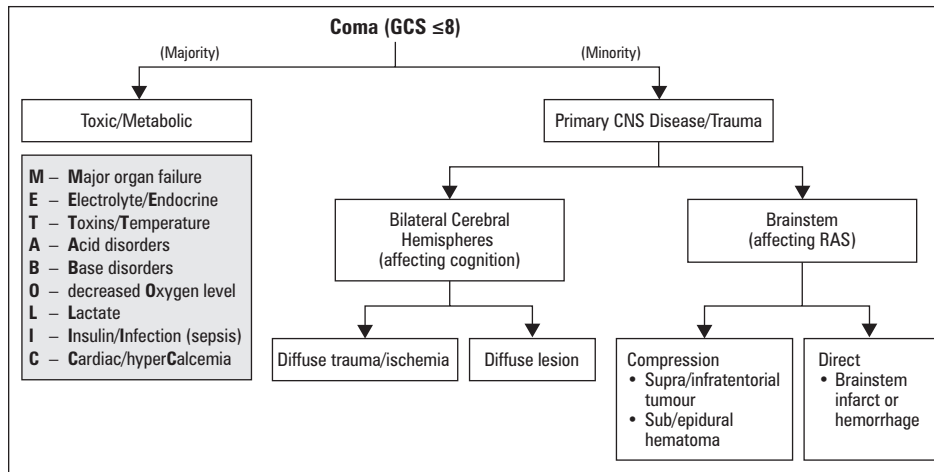


Figure 11. Etiology of Coma



Possible Causes of Coma

AEIOU TIPS

Acidosis/Alcohol
Epilepsy
Infection
Oxygen (hypoxia)/Opiates
Uremia
Temperature/Trauma (especially head)
Insulin (too little or too much)
Psychogenic/Poisoning
Stroke

MANAGEMENT OF ALTERED LOC

History

- obtained from family, friends, police, paramedics, old chart, etc.
- onset and progression
 - abrupt onset suggests CNS hemorrhage/ischemia or cardiac cause
 - progression over hours to days suggests progressive CNS lesion or toxic/metabolic cause
- preceding events
 - it is essential to determine patient's baseline LOC preceding deterioration
 - antecedent trauma, seizure activity, fever
- past medical history (e.g. similar episode, depression, overdose)

Physical Examination

- ABC's, vitals including temperature, cardiac, chest, respiratory, abdominal exam, and the "five Ns" (see sidebar)
- complete neuro exam, in particular examination of the eyes, look for medic alert bracelet

Investigations

- rapid blood sugar, CBC, electrolytes, Cr, BUN, LFTs, glucose, serum osmolality, ABGs, coags, troponins, U/A
- ECG, CXR, CT head
- drug levels of specific toxins if indicated

Diagnosis

- administer appropriate universal antidotes
 - thiamine 100 mg IV if history of EtOH or patient looks malnourished
 - one ampule D50W IV if low blood sugar on finger-prick
 - naloxone 0.4-2 mg IV or IM if opiate overdose suspected
- distinguish between structural and toxic-metabolic coma
 - structural coma
 - pupils, extraocular movements and motor findings, if present, are usually asymmetric
 - look for focal or lateralizing abnormalities
 - toxic-metabolic coma
 - dysfunction at lower levels of the brainstem (e.g. caloric unresponsiveness)
 - respiratory depression in association with an intact upper brainstem (e.g. equal and reactive pupils; see exceptions in Table 11)
 - extraocular movements and motor findings are symmetric or absent



In general, GCS under 8, intubate, but ability to protect airway is primary consideration!



Evaluation of Comatose Patient

Five Ns

Noggin
e.g. raccoon eyes and Battle's sign (bruising of the mastoid process) appears about 8 hours after trauma

Neck
C-spine, neurogenic shock, nuchal rigidity

ENT
Otorrhea, rhinorrhea, tongue biting, odour on breath, hemotympanum

Needles
Inspect for track marks

Neurological
Concentrate on GCS, respiration, posture, movement, pupils, reflexes



Universal Antidotes

DON'T

Dextrose
Oxygen
Naloxone 2 mg
Thiamine 100 mg

- essential to re-examine frequently – status can change rapidly
- diagnosis may become apparent only with the passage of time
 - delayed deficit after head trauma suggestive of epidural hematoma (characteristic “lucid interval”)

Table 11. Toxic – Metabolic Causes of Fixed Pupils

Dilated	Dilated to Normal	Constricted
Anoxia	Hypothermia	Cholinergic agents (e.g. organophosphates)
Anticholinergic agents (e.g. atropine, TCAs)	Barbiturates	Opiates (e.g. heroin), except meperidine
Methanol (rare)	Antipsychotics	
Cocaine		
Opioid withdrawal		
Amphetamines		
Hallucinogens		

Disposition

- readily reversible alteration of LOC: discharge if adequate follow-up care available
- ongoing decreased LOC: admit to service based on tentative diagnosis
- transfer patient if appropriate level of care not available



Chest Pain

**Life Threatening causes of Chest Pain****PET MAP**

Pulmonary embolism
Esophageal rupture
Tamponade
MI/angina
Aortic dissection
Pneumothorax



Imaging is necessary for all suspected aortic dissections, regardless of blood pressure.

**Signs and Symptoms of MI****PULSE**

Persistent chest pain
Upset stomach
Lightheadedness
Shortness of breath
Excessive sweating

**PERC score for PE**

Age > 50 years
HR > 100 bpm
O₂ sat on RA < 94%
Prior history DVT/PE
Recent trauma or surgery
Hemoptysis
Exogenous estrogen
Clinical signs suggesting DVT

Score 1 for each question; a score 0/8 means patient has < 1.6% chance having a PE and avoids further investigation.

Rule Out Life-Threatening Causes

- CVS: acute coronary syndrome/acute MI, pericarditis/cardiac tamponade, aortic dissection
- respiratory: pulmonary embolism (PE)/pneumothorax (tension or spontaneous)
- GI: esophageal rupture/pneumomediastinum

Additional Differential Diagnosis

- cardiac: stable angina
- respiratory: pneumonia
- GI: peptic ulcer disease (PUD), pancreatitis, cholecystitis, esophagitis, reflux, esophageal spasm
- MSK: rib fractures, costochondritis, zoster, etc.
- psychogenic/anxiety (diagnosis of exclusion)

Initial Resuscitation and Management

- O₂, IV, cardiac monitoring, CXR (portable if unstable), ECG

History

- must evaluate cardiac risk factors (DM, HTN, hyperlipidemia, smoking, family history)
- classic presentations (but presentation seldom classic)
 - aortic dissection: syncope with sudden severe tearing pain, often radiating to back, ± focal pain/neurologic loss in extremities secondary to major vessel ischemia
 - pulmonary embolism: pleuritic chest pain (75%), dyspnea, anxiety, tachycardia, PERC SCORE
 - pericarditis: anterior precordial pain, pleuritic, relieved by sitting up and leaning forward
 - acute coronary syndrome (ACS): retrosternal squeezing/pressure pain, radiation to arm/neck, dyspnea, nausea/vomiting, syncope
 - esophageal: frequent heartburn, acid reflux, dysphagia, relief with antacids
- ACS more likely to be atypical in females, diabetics, and >80 years

Physical Examination

- vitals (BP in both arms, but unreliable indicator of dissection)
- palpate chest wall for tender points, but be aware that 25% of patients with acute MI have chest wall tenderness
 - consider a diagnosis of MSK disease only if more serious causes excluded and palpation fully reproduces pain and symptoms
- cardiac exam, respiratory exam, peripheral vascular exam

Investigations

- CBC, electrolytes
- serial cardiac enzymes
 - normal CK-MB does NOT rule out MI
 - troponin I more sensitive (but positive later than CK-MB; can have false positives in renal failure, must follow for 8 hrs post onset of symptoms)
- ECG (see Table 12)
 - always compare with previous
 - PE and acute MI may have normal ECG in up to 50% of cases
 - consider 15-lead ECG if hypotensive or if ECG shows inferior MI or AV node involvement

- CXR
 - always compare with previous
 - PE (see DVT, ER34)
 - ♦ 50% completely normal
 - ♦ atelectasis, elevated hemidiaphragm, pleural effusion
 - aortic dissection (see sidebar ER12 for features)
 - ♦ change from previous CXR is the most accurate finding
 - ♦ CXR is normal in 20% of thoracic dissections
 - pneumothorax
 - ♦ may need inspiration and expiration views
- ABGs – normal in 20% of patients with PE, therefore do not perform
- D-dimer, V/Q scan or helical CT, venous leg Doppler, if PE suspected (see sidebar for *Wells' Score*)
- negative D-dimer rules out PE in low probability patients
- patients with intermediate or high probability Wells' score require imaging

Disposition

- patients at risk of developing dysrhythmias should be admitted to a monitored bed
- consult cardiology for patients with ACS; obtain a cardiothoracic surgery consultation for patients with valvular lesions by echocardiogram, esophageal rupture, or aortic dissection
- discharge is appropriate for patients with a low probability of life-threatening illness due to resolving symptoms and negative workup; instruct the patient to return if they develop SOB or increased chest pain

Table 12. Common Life Threatening ECG Changes

Pathology	ECG Findings
Dysrhythmia	
a) Torsade de Pointes	Ventricular complexes in upward-pointing and downward-pointing continuum (250-350 bpm)
b) Ventricular tachycardia	6 or more consecutive premature ventricular beats (150-250 bpm)
c) Ventricular flutter	Smooth sine wave pattern of similar amplitude (250-350 bpm)
d) Ventricular fibrillation	Erratic ECG tracing, no identifiable waves
Conduction	
a) 2nd degree heart block (Mobitz Type II)	PR interval stable, some QRS's dropped
b) 3rd degree heart block	Total AV dissociation, but stable P-P and R-R intervals
c) Left bundle branch block	Prolonged QRS complex (>0.12s) RSR' in V5 or V6 Monophasic I and V6 May see ST elevation Difficult to interpret, new LBBB is considered STEMI equivalent
Ischemia	
a) STEMI	ST elevation in leads associated with injured area of heart and reciprocal lead changes (depression)
Metabolic	
a) Hyperkalemia	Tall T waves P wave flattening QRS complex widening and flattening
b) Hypokalemia	U waves appear Flattened T waves
Digitalis Toxicity	
	Gradual downward curve of ST At risk for AV blocks and ventricular irritability
Syndromes	
a) Brugada	RBBB with ST elevation in V1, V2 and V3 Susceptible to deadly arrhythmias, including V. Fib.
b) Wellens	Marked T wave inversion in V2 and V3 Left anterior descending coronary stenosis
c) Long QT Syndrome	QT interval longer than ½ of cardiac cycle Predisposed to ventricular arrhythmia

ACUTE MYOCARDIAL INFARCTION

- see *Cardiology*, C25

Management

- immediate stabilization
 - oxygen 4L/min
 - IV access
 - cardiac monitors
 - STAT ECG
 - cardiac enzymes (CK, Troponins)
- ASA 162-325 mg chewed
- nitroglycerin 0.3 mg SL q5min x 3 (IV for CHF, HTN, unresolved pain)
- morphine 2-5 mg IV q5-30min if unresponsive to NTG
- metoprolol 5 mg slow IV q5min x 3 if no contraindication (beware in inferior wall AMI)



Signs of PE on CXR

Westermark's sign: abrupt tapering of a vessel on chest film.

Hampton's hump: a wedge-shaped infiltrate that abuts the pleura.



Wells' Score for PE

Previous Hx of DVT/emboli	+1.5
HR >100	+1.5
Recent immobility or Sx	+1.5
Clinical signs of DVT	+3
Alternate Dx less likely than PE	+3
Hemoptysis	+1
Cancer	+1

Low probability = 0-2

Intermediate probability = 2-6

High probability = >6



Important to look for reciprocal changes in STEMI in order to differentiate from pericarditis (diffuse elevations).



Immediate Treatment of Acute MI

BEMOAN
 Beta-Blockade
 Enoxaparin
 Morphine
 Oxygen
 ASA
 Nitroglycerin

Addition of Clopidogrel to Aspirin and Fibrinolytic Therapy for Myocardial Infarction with ST-Segment Elevation

NEJM 2005; 352(12):1179-1191

Purpose: To assess the benefit of adding clopidogrel to aspirin and fibrinolytic therapy in ST-elevation MI.

Study Characteristics: Double-blind, RCT, following intention-to-treat analysis, with 3491 patients and clinical follow-up at 30 days.

Participants: Individuals presenting within 12 hours of onset of ST-elevation MI (mean age 57, 80.3% male, 50.3% smokers, 9.1% previous MI). Those presenting after 12 hours, age >75, or with previous CABG were excluded.

Intervention: Clopidogrel (300 mg loading dose followed by 75 mg od until day of angiogram) or placebo, in addition to aspirin, a fibrinolytic agent, and heparin when appropriate.

Primary Outcome: Composite of occluded infarct-related artery on angiography (Thrombolysis in Myocardial Infarction flow grade 0 or 1), or death or recurrent MI prior to angiography.

Results: Rates of primary end point were 21.7% in the placebo group and 15.0% in the clopidogrel group (95% CI, 24-47%). Among the individual components of the primary end point, clopidogrel had a significant effect on the rate of an occluded infarct-related artery and the rate of recurrent MI, but no effect on the rate of death from any cause. At 30 days clinical follow-up, there was no difference in rate of death from cardiovascular causes, a significant reduction in the odds of recurrent MI, and a non-significant reduction in recurrent ischemia with need for urgent revascularization. The rates of major bleeding and intracranial hemorrhage were similar between the two groups.

Conclusion: Addition of clopidogrel improves the patency rate of infarct-related arteries and reduces ischemic complications, both of which are associated with improved long-term survival after MI. The trial was not powered to detect a survival benefit and none was seen.

- low molecular weight heparin 1 mg/kg SC bid (30 mg IV STAT post TNK infusion)
- thrombolytics or primary percutaneous coronary intervention (PCI)
 - agents include t-PA, r-PA, Streptokinase, and TNK
 - evaluate indications and contraindications prior to use
- other – antiarrhythmics, cardioversion, defibrillation, transthoracic pacing, angioplasty
- cardiology consult

Epistaxis

- see Otolaryngology, OT27
- 90% of nosebleeds stem from the anterior nasal septum (at Kiesselbach's plexus located in Little's area)
- can be life-threatening

Etiology

- most commonly caused by trauma (digital, blunt, foreign bodies), but can also be caused by barometric changes, nasal dryness, chemicals (cocaine, Otrivin®), or systemic disease (coagulopathies, hypertension, etc.)

Investigations

- CBC, PT/PTT (if indicated)
- x-ray, CT as needed

Treatment

- aim is to localize bleeding and achieve hemostasis
- first-aid: ABC's, lean forward, pinch soft part of nose for 20 minutes
- assess blood loss: vitals, IV normal saline, cross match 2 units packed RBC if significant
- determine site of bleeding: use topical anaesthetic/vasoconstrictor to facilitate; use nasal speculum and good lighting
- attempt to control the bleeding
 - first line: Otrivin® or cocaine
 - second line: cauterize with silver nitrate (one side of septum only!)
 - if these fail, or if bleeding is posterior → nasal packing (must monitor for complications)
 - if packing fails, consult ENT

Disposition

- most patients can be discharged after ensuring vitals are stable, bleeding is controlled and patient has appropriate follow-up
- educate patients about prevention (e.g. humidifiers, saline spray, topical ointments, avoiding irritants, managing hypertension)
- admission may be required for severe cases



Thrombocytopenic patients – use resorbable packs to avoid risk of re-bleeding caused by pulling out the removable pack.



Complications of Nasal Packing
Hypoxemia
Toxic-shock syndrome
Aspiration
Pharyngeal fibrosis/stenosis
Alar/septal necrosis



Headache

- see also Neurology, N39

Etiology

- **the common**
 - common migraine (no aura)/classic migraine (involves aura)
 - ♦ gradual onset, unilateral/bilateral, throbbing
 - ♦ nausea/vomiting, photo/phonophobia
 - ♦ treatment: analgesics, neuroleptics, vasoactive meds
 - tension/muscular headache
 - ♦ never during sleep, gradual over 24 hours
 - ♦ posterior/occipital
 - ♦ increased with stressors
 - ♦ treatment: modify stressor, local measures, NSAIDs, tricyclic antidepressants
- **the deadly**
 - subarachnoid hemorrhage (SAH) (see Neurosurgery, NS17)
 - ♦ sudden onset, increased with exertion
 - ♦ “worst” headache, nausea and vomiting, meningeal signs
 - ♦ diagnosis: CT, LP (5-10% of patients with SAH have negative initial CT)
 - sensitivity of CT decreases with time and is much less sensitive by 48-72 hr
 - ♦ management: urgent neurosurgery consult
 - increased ICP
 - ♦ worst in morning, supine, or bending down
 - ♦ physical exam: neurological deficits, cranial nerve palsies, papilledema
 - ♦ diagnosis: CT scan
 - ♦ management: consult neurosurgery



Note: up to 5% of patients with subarachnoid hemorrhage have a normal CT scan; if suspect SAH with a negative CT, perform a lumbar puncture.



BEWARE: every headache is serious until proven otherwise.



DDx Subarachnoid Hemorrhage
BATS
Berry aneurysm
Arteriovenous malformation/Adult polycystic kidney disease
Trauma
Stroke

- meningitis (see [Infectious Diseases](#), ID6)
 - ♦ flu-like presentation initially (fever, nausea/vomiting, malaise), meningeal signs, purpuric rash
 - ♦ altered level of consciousness and confusion
 - ♦ perform CT to rule out increased ICP then do LP for diagnosis
 - ♦ treatment: early empiric antibiotics (depending on age group), steroid therapy
- temporal arteritis (not immediately deadly but causes great morbidity) (see [Ophthalmology](#), OP38)
 - ♦ unilateral scalp tenderness, jaw claudication, visual disturbances
 - ♦ labs: elevated ESR
 - ♦ temporal artery biopsy is gold standard for diagnosis
 - ♦ treatment: high-dose steroids immediately if TA suspected

**Meningitis**

Do not delay IV antibiotics for LP.

Disposition

- admit if underlying diagnosis is critical or emergent, if there are abnormal neurological findings, if patient is elderly or immunocompromised (atypical presentation), or if pain is refractory to oral medications
- most patients can be discharged with appropriate analgesia and follow up with their family physician; instruct patients to return for fever, vomiting, neurologic changes, or increasing pain

Joint Pain

- see [Rheumatology](#)

Rule Out Life-Threatening Causes

- septic joint (see [Orthopaedics](#), OR8)

Differential Diagnosis

- articular pain
 - monoarticular
 - ♦ infectious: bacterial, viral, fungal
 - ♦ hemarthrosis: trauma/fracture, anticoagulants, bleeding diatheses
 - ♦ crystal induced: gout, CPPD, hydroxyapatite
 - ♦ inflammatory: seropositive, seronegative
 - ♦ neoplasm
 - ♦ degenerative: osteoarthritis
 - polyarticular
 - ♦ infectious: Lyme disease, bacterial endocarditis, septicemia, *gonococcus*, viral
 - ♦ post-infectious: rheumatic fever, reactive arthritis, enteric infections
 - ♦ inflammatory: seropositive, seronegative
 - ♦ degenerative: osteoarthritis
- non-articular
 - musculoskeletal
 - ♦ localized: tendonitis, bursitis, capsulitis, muscle sprain
 - ♦ generalized: fibromyalgia, PMR
- other
 - neurologic: spinal stenosis/spondylolithesis, degenerative disc disease, cauda equina syndrome, neoplasm, thoracic outlet syndrome, Charcot joint
 - vascular: intermittent claudication

**Causes of Joint Pain****SOFTER TISSUE**

Sepsis
 Osteoarthritis
 Fractures
 Tendon/muscle
 Epiphyseal
 Referred

 Tumour
 Ischemia
 Seropositive arthritides
 Seronegative arthritides
 Urate
 Extra-articular rheumatism
 (e.g. polymyalgia)

History and Physical Examination

- determine onset, course, location, character of the pain (OPQRST) and recurrence
- determine which joint or joints are involved
- associated symptoms: fever, constitutional symptoms, skin lesions, conjunctivitis, urethritis
- patterns of joint involvement: polyarticular vs. monoarticular, symmetric vs. asymmetric
- inflammatory symptoms: prolonged morning stiffness, stiffness and pain ease through the day, midday fatigue, soft tissue swelling
- non-inflammatory symptoms: stiffness short lived after inactivity, short duration stiffness in the morning, pain increases with activity
- assess ROM, presence of joint effusion, warmth
- watch for: localized joint pain, erythema, warmth, swelling with pain on active ROM, inability to bear weight, fever as these may indicate presence of septic joint

Investigations

- x-ray, CBC, ESR, CRP, WBC, INR/PTT, blood cultures, urate
- joint aspirate → send for: WBC, protein, glucose, Gram stain, crystals

Management

- septic joint: IV antibiotics \pm joint decompression and drainage
 - antibiotics can be started empirically if septic arthritis cannot be ruled out
- crystalline synovitis: NSAIDs at high dose, colchicine within first 24 hours, corticosteroids
 - do not use allopurinol, as it may worsen acute attack
- acute polyarthritis: NSAIDs, analgesics (acetaminophen \pm opioids), corticosteroids local or systemic
 - hospitalization is required in the presence of (1) significant, concomitant internal organ involvement; (2) signs of bacteremia, including vesiculopustular skin lesions, Roth spots, shaking chills, or splinter hemorrhages; (3) systemic vasculitis; (4) severe pain; (5) severe constitutional symptoms; (6) purulent synovial fluid in one or more joints; or (7) immunosuppression
- osteoarthritis: acutely: NSAIDs, acetaminophen
- soft tissue pain: allow healing with enforced rest \pm immobilization
 - nonpharmacologic treatment: local heat or cold, electrical stimulation, massage
 - pharmacologic: oral analgesics, NSAIDs, muscle relaxants, corticosteroid injections, topical agents

Otalgia

Differential Diagnosis (see also Otolaryngology, OT6)

- local
 - infections: AOE, AOM, OM with effusion, mastoiditis, myringitis, malignant otitis in diabetics, herpes simplex/zoster, auricular cellulites, external canal abscess
 - others: trauma, neoplasm, foreign body, cerumen impactions, Wegener's
- determine onset, course, location and character of pain
- otorrhea, aural fullness, hearing loss, pruritis
- Q-tip use, hearing aids, headphones
- associated symptoms: fever
- observe for otorrhea, palpation of outer ear, otoscope to see bulging erythematous TM, perforation

Investigations

- consider audiogram if hearing loss

Management

- debridement and antibiotics for cerumen and infection



Seizures

- see Neurology, N8

Definition

- paroxysmal alteration of behaviour and/or EEG changes resulting from abnormal, excessive activity of neurons

Categories

- generalized seizure (consciousness always lost): tonic/clonic, absence, myoclonic, atonic
- partial seizure (focal): simple partial, complex partial
- causes: trauma, intracranial hemorrhage, structural abnormality, infection, toxins/drugs, metabolic disturbance (hypo/hyperglycemia, hypo/hyponatremia, hypocalcemia, hypomagnesemia); primary seizure disorder
- differential diagnosis: syncope, pseudoseizures, migraines, movement disorder, narcolepsy/cataplexy, myoclonus

History

- from patient and bystander: flaccid and unconscious, often with deep rapid breathing
- preceding aura, rapid onset, loss of bladder/bowel control, tongue-biting (sides of the tongue)

Physical Examination

- injuries to head and spine and bony prominences (e.g. elbows), tongue laceration, aspiration, urinary incontinence

Investigations

- known seizure disorder: anticonvulsant levels
- Accu-Chek®
- first time seizure: CBC, serum glucose, electrolytes, BUN, creatinine, Ca, Mg; consider prolactin, β -hCG, tox screen
- initial: CT; x-ray if suspected extremity injuries. Definitive: MRI, EEG



Min. Workup in an Adult with 1st Time Seizure
 CBC and diff
 Electrolytes including Ca, Mg, PO₄
 Head CT

Table 13. Management of Status Epilepticus

Time (min)	Steps
0-5	Give oxygen; ensure adequate ventilation Monitor: vital signs, electrocardiography, oximetry Establish IV access; obtain blood samples for glucose level, CBC, electrolytes, toxins, and anticonvulsant levels
6-9	Give 50 mL 50% glucose (preceded by thiamine 100 mg IM in adults)
10-20	IV lorazepam 0.1 mg/kg at 2 mg/min or IV diazepam 0.2 mg/kg at 5 mg/min Diazepam can be repeated if seizures do not stop after 5 min; if diazepam is used to stop the status, then phenytoin should be administered promptly to prevent the recurrence of status
21-60	If status persists, administer 15-20 mg/kg of phenytoin intravenously no faster than 50 mg/min in adults and 1 mg/kg/min in children
>60	If status does not stop after 20 mg/kg of phenytoin, give additional doses of 5 mg/kg to a maximal dose of 30 mg/kg. If status persists, then give 20 mg/kg of phenobarbital IV at 100 mg/min. When phenobarbital is given after a benzodiazepine, ventilatory assistance is usually required If status persists, then give general anaesthesia (e.g., pentobarbital). Vasopressors or fluid volume are usually necessary. Electroencephalogram should be monitored. Neuromuscular blockade may be needed.

Adapted from: *Cecil's Essentials of Medicine*, 7th edition, Table 125-7. Used with permission.

Disposition

- the decision to admit or discharge should be based on the underlying disease process identified
 - if a patient has returned to baseline function and is neurologically intact, then consider discharge with outpatient follow-up
- first-time seizure patients being discharged should be referred to a neurologist for follow-up
- admitted patients should generally have a neurology consult
- patient should not drive until medically cleared (local regulations vary)
 - complete notification form to appropriate authority re: ability to drive
- warn regarding other safety concerns (e.g. no swimming, bathing children alone, etc.)

Shortness of Breath

- see [Respirology](#) and [Cardiology](#)

Etiology

- categorized into one of two groups: respiratory or cardiovascular
- respiratory system dyspnea: discomfort related to disorders of the central controller (brain), the ventilatory pump (ventilatory muscles, peripheral nerves), and the gas exchanger (alveoli and pulmonary capillaries)
- cardiovascular system dyspnea: cardiac diseases (acute ischemia, heart failure, systolic dysfunction, valvular disorders, pericardial diseases), anemia, and deconditioning

History/Physical

- acute SOB is often due to a relatively limited number of conditions. Associated symptoms and signs are key to the appropriate diagnosis
 - substernal chest pain with cardiac ischemia
 - fever, cough and sputum with respiratory infections
 - urticaria with anaphylaxis
 - wheezing with acute bronchospasm
- dyspnea may be the sole complaint and the physical examination may reveal few abnormalities (e.g. pulmonary embolism, pneumothorax)
- chest tightness may be indicative of bronchospasm
- a sensation of rapid, shallow breathing may correspond to interstitial disease
- a sense of heavy breathing is typical of deconditioning
- vitals including pulse oximetry
 - wheeze (airway) vs. crackles (parenchymal), JVP, and murmurs

Investigations

- CBC + differential (hematocrit to exclude anemia), electrolytes, consider ABG
- CXR (hyperinflation and bullous disease suggestive of obstructive lung disease, or changes in interstitial markings consistent with inflammation, infection or interstitial fluid)
- serial cardiac enzymes and ECG if considering cardiac source
- CT chest usually is not indicated in the initial evaluation of patients with dyspnea, but can be valuable in patients with interstitial lung disease, occult emphysema, or chronic thromboembolic disease (PE)

Disposition

- the history and physical examination lead to accurate diagnoses in patients with dyspnea in approximately two-thirds of cases; the decision to admit or discharge should be based on the underlying disease process identified
 - consideration for intubation should be early in CO₂ retainers (e.g. COPD)
- if the decision to discharge is chosen, provide appropriate discharge instructions to return in case of returning/worsening SOB



If administering phenytoin, patient must be on a cardiac monitor as arrhythmias and/or hypotension may occur.



Causes of Acute Dyspnea

Cardiovascular: acute MI, CHF, cardiac tamponade.

Respiratory: bronchospasm, pulmonary embolism, pneumothorax, infection (bronchitis, pneumonia), upper airway obstruction (aspiration, anaphylaxis).



Contraindication to 100% Oxygen
CO₂ retainers (e.g. COPD).



Syncope



5 Types of Syncope

1. Vasomotor
2. Cardiac
3. CNS
4. Metabolic
5. Psychogenic



Causes of Syncope by System

HEAD, HEART, VeSSELS

Hypoxia/Hypoglycemia
Epilepsy
Anxiety
Dysfunctional brainstem

Heart attack
Embolism (PE)
Aortic obstruction
Rhythm disturbance
Tachycardia

Vasovagal
Situational
Subclavian steal
ENT (glossopharyngeal neuralgia)
Low systemic vascular resistance
Sensitive carotid sinus

Definition

- sudden, transient loss of consciousness and postural tone with spontaneous recovery
- usually caused by generalized cerebral or reticular activating system hypoperfusion

Etiology

- cardiogenic: arrhythmia, outflow obstruction (e.g. PE, tamponade, tension pneumothorax, pulmonary HTN), MI, valvular disease
- non-cardiogenic: peripheral vascular (hypovolemia), vaso-vagal, cerebrovascular disorders, CNS, metabolic disturbances (e.g. EtOH intoxication)

History

- gather details from witnesses, and clarify patient's experience (e.g. dizziness, ataxia, or true syncope)
- distinguish between syncope and seizure (see Neurology, N9)
 - some patients may have myoclonic jerks with syncope – NOT a seizure
 - signs and symptoms during presyncope, syncope and postsyncope
 - past medical history, drugs
 - think anatomically in differential; pump (heart), blood (quality), vessels, brain
- sudden loss of consciousness with no warning or prodrome is cardiogenic until proven otherwise

Physical Examination

- postural BP and HR
- cardiovascular, respiratory and neuro exam
- physical findings in the elderly patient who falls (**I HATE FALLING**):
 - Inflammation of joints (or joint deformity)
 - Hypotension (orthostatic blood pressure changes)
 - Auditory and visual abnormalities
 - Tremor (Parkinson's disease or other causes of tremor)
 - Equilibrium (balance) problem
 - Foot problems
 - Arrhythmia, heart block or valvular disease
 - Leg-length discrepancy
 - Lack of conditioning (generalized weakness)
 - Illness
 - Nutrition (poor; weight loss)
 - Gait disturbance

Investigations

- ECG (tachycardia, bradycardia, blocks, WPW, long QT interval), bedside glucose
- as indicated: CBC, electrolytes, BUN, creatinine, ABGs, Troponin, Ca, Mg, β -hCG
- consider drug screen

Management

- ABCs, IV, O₂, monitor
- examine for signs of trauma caused by syncopal episode
- cardiogenic syncope: admit to medicine/cardiology
- non-cardiogenic syncope: discharge with follow-up as indicated by cause

Disposition

- decision to admit is based on etiology
- most patients will be discharged
- on discharge, instruct patient to follow up with family physician
 - educate re: avoiding orthostatic or situational syncope
 - patients with recurrent syncope should avoid high-risk activities (e.g. driving)



Sexual Assault



Legally required to report sexual assault if victim is <16 years of age to Children's Aid Society (CAS).

Epidemiology

- 1 in 4 women and 1 in 10 men will be sexually assaulted in their lifetime
- it is estimated that only 7% of rapes are reported

General Approach

- ABCs, treat acute, serious injuries
- ensure patient is not left alone and provide ongoing emotional support
- set aside adequate time for exam (usually 1.5 hours)

- obtain consent for medical exam and treatment, collection of evidence, disclosure to police (notify police as soon as consent obtained)
- Sexual Assault Kit (document injuries, collect evidence) if <72 hrs since assault
- label samples immediately and pass directly to police
- offer community crisis resources (e.g. shelter, hotline)
- do not report unless victim requests (legally required if <16 years old)

History

- ensure privacy for the patient – others should be asked to leave
- questions to ask: who? how many? when? where did penetration occur? what happened? any weapons or physical assault?
- post-assault activities (urination, defecation, change of clothes, shower, douche, etc.)
- gynecologic history
 - gravity, parity, last menstrual period
 - contraception use
 - last voluntary intercourse (sperm motile 6-12 hours in vagina, 5 days in cervix)
- medical history – acute injury/illness, chronic diseases, psychiatric history, medications, allergies, etc.

Physical Examination

- evidence collection is always secondary to treatment of serious injuries
- never re-traumatize a patient with the examination
- general examination
 - mental status
 - sexual maturity
 - patient should remove clothes and place in paper bag
 - document abrasions, bruises, lacerations, torn frenulum/broken teeth (indicates oral penetration)
- pelvic exam and specimen collection
 - ideally before urination or defecation
 - examine for seminal stains, hymen, signs of trauma
 - collect moistened swabs of dried seminal stains
 - pubic hair combings and cuttings
 - speculum exam
 - ♦ lubricate with water only
 - ♦ vaginal lacerations, foreign bodies
 - ♦ Pap smear
 - ♦ oral/cervical/rectal culture for gonorrhea and chlamydia
 - ♦ posterior fornix secretions if present or aspiration of saline irrigation
 - ♦ immediate wet smear for motile sperm
 - ♦ air-dried slides for immotile sperm, acid phosphatase, ABO group
- others
 - fingernail scrapings
 - saliva sample from victim

Investigations

- VDRL – repeat in 3 months if negative
- serum β -hCG
- blood for ABO group, Rh type, baseline serology (e.g. hepatitis, HIV)

Management

- involve local/regional sexual assault team
- medical
 - suture lacerations
 - tetanus prophylaxis
 - gynecology consult for foreign body, complex lacerations
 - assumed positive for gonorrhea and chlamydia
 - ♦ management: azithromycin 1 g PO x 1 dose (alt: doxycycline 100 mg PO bid x 7 days) and cefixime 400 mg PO x 1 dose
 - may start prophylaxis for hepatitis B and HIV
 - pre and post counselling for HIV testing
 - pregnancy prophylaxis offered
 - ♦ levonorgestrel 0.75 mg PO STAT, repeat within 12 hours (Plan B®)
- psychological
 - high incidence of psychological sequelae
 - have victim change and shower after exam completed

Disposition

- discharge if injuries/social situation permit
- follow-up with MD in rape crisis centre within 24 hours
- best if patient does not leave ED alone



Risk of Sexually Transmitted Disease After Sexual Assault

Gonorrhea: 6-18%
Chlamydia: 4-17%
Syphilis: 0.5-3%
HIV: <1%



How do you get a patient who is accompanied by her partner alone without arousing suspicion?
Order an x-ray.

DOMESTIC VIOLENCE

- women are usually the victims, but male victimization also occurs
- identify the problem (need high index of suspicion)
 - suggestive injuries (bruises, sprains, abrasions, occasionally fractures, burns or other injuries; often do not match up with history provided)
 - somatic symptoms (chronic and vague complaints)
 - psychosocial symptoms
 - clinician impression (your 'gut feeling', e.g. overbearing partner that won't leave patient's side)
- if disclosed, be supportive and assess danger
- order an x-ray to secretly get patient alone to question re: abuse
- patient must consent to follow-up investigation/reporting (unless for children)

Management

- treat injuries
- ask about sexual assault and children at home
- document findings
- safety plan
- follow-up: family doctor/social worker



Medical Emergencies

Anaphylaxis and Allergic Reactions



Most Common Triggers for Anaphylaxis

- Penicillin
- Stings
- Nuts
- Shellfish

Etiology

- exaggerated immune response classically IgE mediated, sensitization then re-exposure
- anaphylaxis: a severe hypersensitivity reaction affecting at least two organ systems (e.g. GI, derm, resp)
- urticaria: a hypersensitivity reaction causing an itchy skin eruption
- angioedema: swelling that occurs in the tissue just below the surface of the skin, most often around the lips and eyes
- anaphylactoid reaction: non-IgE mediated, may occur with first exposure (e.g. radiocontrast dyes); presentation and treatment same as for anaphylaxis

History and Physical Examination

- general – marked anxiety, apprehension, tremor, cold sensation
- skin – generalized urticaria, edema, erythema, pruritus
- GI – abdominal pain, nausea, vomiting, diarrhea (most allergens are ingested, therefore GI symptoms common)
- respiratory – nasal congestion, sneezing, coryza, cough, hoarseness, sensation of throat tightness, dyspnea, stridor, wheeze
- eyes – itch, tearing, conjunctival injection
- cardiovascular – hypotension, tachycardia, weakness, dizziness, syncope, chest pain, arrhythmia, MI

Management

- remove causative agent; secure ABCs
- epinephrine
 - on scene – epi-pen (injectable epinephrine) if available
 - moderate signs and symptoms (minimal airway edema, mild bronchospasm, cutaneous reactions)
 - ♦ adult: 0.3-0.5 mL of 1:1000 solution IM epinephrine
 - ♦ child: 0.01 mL/kg/dose up to 0.4 mL/dose 1:1000 epinephrine
 - severe signs and symptoms (laryngeal edema, severe bronchospasm and shock, severe hypotension)
 - ♦ epinephrine via IV or ETT starting at 1 mL of 1:10,000 (0.1 mg) in adults; 0.01 mL/kg in children
 - ♦ cardiac monitoring, ECG
- diphenhydramine (Benadryl®) 50 mg IM or IV q4-6h
- methylprednisolone 50-100 mg IV (dose depending on severity)
- salbutamol (Ventolin®) via nebulizer if bronchospasm
- glucagon (for those on β -blockers with resistant hypotension and/or cardiac disease) 5-15 μ g q1min IV

Disposition

- monitor for 4-6 hours in ED (minimum) and arrange follow up with family physician in 24-48 hours
- can have second phase (rebound) reaction up to 48 hours later, patient may need to be supervised
- 3-day course of:
 - H₁ antagonist (cetirizine 10 mg PO od)
 - H₂ antagonist (ranitidine 150 mg PO od)
 - corticosteroid (prednisone 50 mg PO od)



Treatment

- Airway control
- Epinephrine
- Establish IV and give fluids
- Steroids
- Anti-histamines

Asthma

- see Respirology, R7
- chronic inflammatory airway disease with episodes of bronchospasm and inflammation resulting in reversible airflow obstruction

Investigations

- O₂ sat
- peak flow meter
- \pm ABG (only in life threatening exacerbations)
- CXR if diagnosis in doubt or concerns of pneumonia, pneumothorax, etc.

Table 14. Asthma Assessment and Management

Classifications	History and Physical Examination	Management
Respiratory Arrest Imminent	<ul style="list-style-type: none"> • Exhausted, confused, diaphoretic, cyanotic • Silent chest, ineffective respiratory effort • Decreased HR • O₂ sat <90% despite supplemental O₂ 	<ul style="list-style-type: none"> • 100% O₂, cardiac monitor, IV access • Intubate (consider pre-induction with ketamine) • β-agonist: MDI 4–8 puffs OR nebulizer 5 mg continually • Anticholinergics: MDI 4–8 puffs q20 min x 3 OR nebulizer 0.5 mg q20 min x 3 • IV steroids: methylprednisolone 125 mg, hydrocortisone 500 mg
Severe Asthma	<ul style="list-style-type: none"> • Agitated, diaphoretic, laboured respirations • Difficulty speaking in full sentences • No relief from β-agonist • O₂ sat <90%, FEV₁ <50% 	<ul style="list-style-type: none"> • Anticipate need for intubation • Similar to above management (β-agonist may be less frequent; q15-20 min) • Magnesium sulphate 2 g IV
Moderate Asthma	<ul style="list-style-type: none"> • SOB at rest, cough, congestion, chest tightness • Nocturnal symptoms • Inadequate relief from β-agonist • FEV₁ 50-80% 	<ul style="list-style-type: none"> • O₂ to achieve O₂-sat >90% • β-agonist: puffer of neb q1h • Steroids: prednisone 40-60 mg PO • Anticholinergics (Atrovent)
Mild Asthma	<ul style="list-style-type: none"> • Exertional SOB/cough with some nocturnal symptoms • Good response to β-agonist • FEV₁ >80% 	<ul style="list-style-type: none"> • β-agonist • Monitor FEV₁ • Consider steroids (nebulized or PO)

Disposition

- β -agonist MDI regular use (2-4 puffs q2-4h) until symptoms controlled then prn
- prednisone 30-60 mg/day for 7-14 days with no taper
- inhaled steroid
- follow-up with primary care physician

Cardiac Dysrhythmias

- see Cardiology, C12

Bradyarrhythmias and AV Conduction Blocks

- AV conduction blocks
 - 1st degree – prolonged PR interval (>200 msec), no treatment required
 - 2nd degree
 - ♦ Mobitz I – gradual prolongation of PR then dropped QRS, usually benign
 - ♦ Mobitz II – PR constant with dropped QRS, can progress to 3rd degree AV block
 - 3rd degree – P unrelated to QRS, PP and RR intervals constant
 - ♦ atropine and transcutaneous pacemaker (TCP)
 - ♦ if TCP fails consider dopamine, epinephrine IV
 - long term treatment for Mobitz II and 3rd degree block – internal pacemaker
- sinus bradycardia (rate <60 bpm)
 - can be normal (especially in athletes)
 - causes: vagal stimulation, vomiting, myocardial infarction/ischemia, increased ICP, sick sinus node, hypothyroidism, drugs (e.g. β -blockers, CCBs)
 - treat if symptomatic (hypotension, chest pain)
 - ♦ acute: atropine \pm transcutaneous pacing
 - ♦ sick sinus: transcutaneous pacing
 - ♦ drug induced: discontinue/reduce offending drug



Beware of the silent asthmatic! This is a medical emergency and may require emergency intubation.



5 Essential Elements on History

- Cause of exacerbation
- Previous ER/ICU visits
- Previous intubations
- Timing of recent steroid use
- Frequency of asthma medication use



Treatment of Asthma

ASTHMA

Adrenergics (beta-agonists)

STeroids

Hydration

Mask (O₂)

Antibiotics (if concurrent infection)



Atropine is unlikely to work in 3rd degree heart block.



If the patient with tachyarrhythmia is unstable, perform immediate cardioversion.



Clinical Features of Instability

- Hypotension (sBP <90)
- CHF or pulmonary edema
- Chest pain
- Altered LOC (may indicate shock)



If patient has Wolff-Parkinson-White and is in AFib use amiodarone or procainamide. Avoid AV nodal blocking agents (adenosine, digoxin, diltiazem, verapamil) as this can increase conduction through bypass tract.



Use the CHADS2 score from Table 3, Cardiology, C17

Supraventricular Tachyarrhythmias (narrow QRS)

- sinus tachycardia (rate >100 bpm)
 - causes: increased sympathetic tone, drugs, fever, hypotension, anemia, thyrotoxicosis, MI, PE, emotional, pain, etc.
 - treat underlying cause, consider β -blocker if symptomatic
- regular rhythm
 - vagal manoeuvres (carotid massage, Valsava), adenosine 6 mg IV push, if no conversion give 12 mg, can repeat 12 mg dose once
 - rhythm converts: probable re-entry tachycardia
 - ♦ monitor for recurrence
 - ♦ treat recurrence with adenosine or longer acting medications
 - rhythm does not convert: atrial flutter, ectopic atrial tachycardia, junctional tachycardia
 - ♦ rate control (diltiazem, β -blockers) and consult cardiology
- irregular rhythm
 - probable atrial fibrillation, atrial flutter or multifocal atrial tachycardia
 - rate control (diltiazem, β -blockers)

Atrial Fibrillation

- most common sustained arrhythmia; no organized P waves, irregularly irregular heart rate, narrow QRS (typically)
- etiology: HTN, CAD, thyrotoxicosis, EtOH (holiday heart), valvular disease, pericarditis, cardiomyopathy, Sick Sinus Syndrome
- treatment principles: stroke prevention, treat symptoms, identify/treat underlying cause
- decreases cardiac output by 20-30% (due to loss of organized atrial contractions)
- acute management
 - if onset of AFib is >24-48 hrs: anticoagulate 3 wks prior to and 4 wks after cardioversion or do transesophageal echo to rule out clot
 - if symptomatic or first presentation – cardiovert
 - ♦ electrical cardioversion: synchronized DC cardioversion
 - ♦ chemical cardioversion: amiodarone, procainamide, flecainide, propafenone (if decreased LV function use amiodarone)
- long term management: rate or rhythm control, consider anticoagulation (CHADS2)

Ventricular Tachyarrhythmias (wide QRS)

- ventricular tachycardia (VT) (rate usually 140-200 bpm)
 - definition: 3 or more consecutive ventricular beats at >100 bpm
 - etiology: CAD with MI is most common cause
 - treatment: sustained VT (>30 seconds) is an emergency
 - ♦ hemodynamic compromise: DC cardioversion
 - ♦ no hemodynamic compromise: DC cardioversion, lidocaine, amiodarone, procainamide
- ventricular fibrillation – call a code blue, follow ACLS for pulseless arrest
- torsades de pointes
 - looks like VT but QRS ‘rotates around baseline’ with changing axis and amplitude (twisted ribbon)
 - etiology: prolonged QT due to drugs (e.g. quinidine, TCAs, erythromycin, quinolones), electrolyte imbalance (hypokalemia, hypomagnesemia), congenital
 - treatment:
 - ♦ IV Mg, temporary overdrive pacing, isoproterenol
 - ♦ correct cause of prolonged QT
 - ♦ discontinue cardioversion if hemodynamic compromise

Chronic Obstructive Pulmonary Disease (COPD)

- see [Respirology](#), R8
- progressive development of irreversible airway obstruction, typically caused by smoking
- acute exacerbation: episode of increased dyspnea, coughing, increase in sputum volume or purulence

History and Physical Examination

- worsening dyspnea or tachypnea
- acute change in frequency, quantity and colour of sputum production
- trigger: pneumonia, urinary tract infection, PE, CHF, MI, drugs

Investigations

- CBC, electrolytes, ABG, CXR, ECG, PFTs

Management

- keep O₂ sat 88-92% (beware of CO₂ retainers, but do not withhold O₂ if hypoxic)
- ipratropium is bronchodilator of choice, add salbutamol
- steroids: prednisone 40 mg PO (tapered over 3 weeks)
- antibiotics: TMP-SMX, cephalosporins, respiratory quinolones (if signs of infection)
- ICU admission if life-threatening with ventilation (chance of ventilation dependency)
- lower threshold to admit if co-morbid illness



Need to Rule Out with COPD Exacerbation

- Pneumothorax
- CHF exacerbation
- Acute MI
- Pneumonia and other infectious causes
- Pulmonary embolus

Disposition

- can use up to 4-6 puffs qid of ipratropium and salbutamol for exacerbations
- continue antibiotics if started and give tapering steroids

Congestive Heart Failure

- also see Cardiology, C32

Etiology

- decreased myocardial contractility: ischemia, infarction, cardiomyopathy, myocarditis
- pressure overload states: hypertension, valve abnormalities, congenital heart disease
- restricted cardiac output: myocardial infiltrative disease, cardiac tamponade
- volume overload

Causes of Exacerbation or Precipitants

- cardiac: acute myocardial infarction or ischemia, cardiac tachyarrhythmias (e.g. atrial fibrillation), uncontrolled hypertension
- medications: non-compliance with or change in cardiac medications, NSAIDs, steroids
- dietary: increased sodium intake
- increased cardiac output demand: infection, anemia, hyperthyroidism, pregnancy
- other: pulmonary embolus, physical overexertion, renal failure

History/Presentation

- left-sided heart failure
 - dyspnea, decreased exercise tolerance, paroxysmal nocturnal dyspnea, orthopnea, nocturia, fatigue, possibly altered mental status, syncope, systemic hypotension
 - in severe cases pulmonary edema: severe respiratory distress, pink frothy or white sputum, rales, S3 or S4
- right-sided heart failure
 - dependent edema, jugular venous elevation, hepatic enlargement, ascites
- patients often present with a combination of right-sided and left-sided symptoms

Physical Examination

- vitals: tachypnea, tachycardia, hypo- or hypertension, hypoxia
- respiratory: crackles (acute), wheeze (chronic)
- cardiac: laterally displaced apex, S3 or S4, jugular venous distention, hepato-jugular reflex
- abdominal: hepatomegaly, ascites
- peripheral vascular: peripheral or sacral edema, weak peripheral pulses, pulsus alternans (alternating weak and strong pulse), cool extremities

Investigations

- labs: CBC, electrolytes, AST, ALT, bilirubin, creatinine, BUN, cardiac enzymes, BNP (brain natriuretic peptide)
- chest X-ray (see side bar)
- ECG: look for MI, ischemia
 - in CHF: LVH, atrial enlargement, conduction abnormalities
- ABG: if severe or refractory to treatment
 - hypoxemia, hypercapnia and acidosis are signs of severe CHF
- echocardiogram: not usually used in emergency evaluation, previous results may aid in diagnosis
- may be precipitated by arrhythmia (e.g. sudden onset AFib) – correct if new

Management (acute)

- ABC, may require intubation if severe hypoxia
- sit upright, cardiac monitoring and continuous pulse oximetry
- saline lock IV, Foley catheter (to follow effectiveness of diuresis)
- 100% O₂ by mask
 - if poor response may require CPAP, BiPAP, or intubation
- drugs
 - nitro 0.3 mg SL q5min PRN ± topical nitro patch (0.2-0.8 mg/hr)
 - ♦ if not responding or ischemia: 10-200 µg/min IV, titrate
 - diuretic if volume overloaded (e.g. furosemide 40-80 mg IV)
 - morphine 1-2 mg IV prn
 - ♦ if hypotensive: dobutamine (2.5 µg/kg/min IV) or dopamine (5-10 µg/kg/min IV), titrate up to sBP 90-100
 - ASA 160 mg chew and swallow
- treat precipitating factor
- cardiology or medicine consult

**Causes of CHF Exacerbation****FAILURE**

Forgot medication
 Arrhythmia/Anemia
 Ischemia/Infarction/Infection
 Lifestyle (e.g. too much salt)
 Upregulation of cardiac output (pregnancy, hyperthyroidism)
 Renal failure
 Embolism (pulmonary)

**Hospital Management Required if:**

- Acute MI
- Pulmonary edema or severe respiratory distress
- Severe complicating medical illness (e.g. pneumonia)
- Anasarca
- Symptomatic hypotension or syncope
- Refractory to outpatient therapy
- Thromboembolic complications requiring interventions
- Clinically significant arrhythmias
- Inadequate social support for safe outpatient management
- Persistent hypoxia requiring supplemental oxygen

**CHF on CXR**

Pulmonary vascular redistribution
 Perihilar infiltrates
 Interstitial edema, Kerley B lines
 Alveolar edema, bilateral infiltrates
 May see cardiomegaly, pleural effusions

**Acute Treatment of CHF****LMNOP**

Lasix (furosemide)
 Morphine
 Nitroglycerine
 Oxygen
 Position (sit upright)

DVT and Pulmonary Embolism



Risk Factors for VTE THROMBOSIS

Trauma, travel
Hypercoagulable, HRT
Recreational drugs (IVDU)
Old (age > 60)
Malignancy
Birth control pill
Obesity, obstetrics
Surgery, smoking
Immobilization
Sickness (CHF, MI, nephrotic syndrome, vasculitis)



PERC score for PE

Age > 50 years
HR > 100 bpm
O₂ sat on RA < 94%
Prior history DVT/PE
Recent trauma or surgery
Hemoptysis
Exogenous estrogen
Clinical signs suggesting DVT

Score 1 for each question; a score 0/8 means patient has < 1.6% chance having a PE and avoids further investigation.



Wells Score for PE

Previous Hx of DVT/emboli	+1.5
HR > 100	+1.5
Recent immobility or Sx	+1.5
Clinical signs of DVT	+3
Alternate Dx less likely than PE	+3
Hemoptysis	+1
Cancer	+1

Low probability = 0-2
Intermediate probability = 2-6
High probability = > 6



D-dimer is only useful if it is negative.
Negative predictive value > 99%.



50% of patients with symptomatic proximal DVT will develop PE, often within days to weeks of the event.

- see also [Respirology](#), R18

Risk Factors

- Virchow's triad
 - alterations in blood flow (venous stasis)
 - injury to endothelium
 - hypercoagulable state (including pregnancy, use of OCP, malignancy)
- most significant risk factors (see side bar for complete list)
 - major surgery or trauma or prolonged hospitalization
 - permanent immobilization and age
 - malignancy, other hypercoagulable state
 - prior venous thromboembolism

History/Presentation

- DVT: calf pain, leg swelling/erythema/edema, palpable cord on exam; can be asymptomatic
- PE: dyspnea, pleuritic chest pain, tachypnea, hemoptysis, cyanosis, hypoxia, fever
- presence of risk factors and family history of venous thromboembolic disease
- clinical signs/symptoms are unreliable for diagnosis and exclusion of DVT/PE; investigation often needed (see Figures 12 and Figure 13)
- calculate the PERC score to assess the need for PE work-up before assessing the likelihood of a PE (Well's criteria)

Investigations (Figures 12-14)

- ECG and CXR are useful to look for other causes (e.g. ACS, pneumonia)
- D-dimer is only useful if it is negative in low risk patients
- Ultrasound has high sensitivity and specificity for proximal clot but only 73% sensitivity for DVT below the knee
- CT angiography has high sensitivity and specificity for PE, may also suggest other etiology
- V/Q scan useful when CT angio not available, or patient unable to tolerate IV contrast (e.g. renal failure, allergy)

Management of DVT/PE

- LMWH unless patient also has renal failure
 - dalteparin 200 IU/kg SC q24h or enoxaparin 1.5 mg/kg SC q24h
- warfarin started at same time as LMWH (5 mg PO daily initially)
- LMWH discontinued when INR has been therapeutic (2-3) for 2 consecutive days
 - early ambulation with analgesia is safe if appropriately anticoagulated
- IVC filter or surgical thrombectomy considered if anticoagulation is contraindicated
- consider thrombolysis if extensive DVT or PE causing hemodynamic compromise
 - often can be treated as outpatient, may require analgesia for chest pain (narcotic or NSAID)
- admit if hemodynamically unstable, require supplemental O₂, major comorbidities, lack of sufficient social supports, unable to ambulate, need invasive therapy
- long term anticoagulation
 - if reversible risk factor: 3-6 months of warfarin
 - idiopathic VTE: may need longer term warfarin (5 yrs or more)

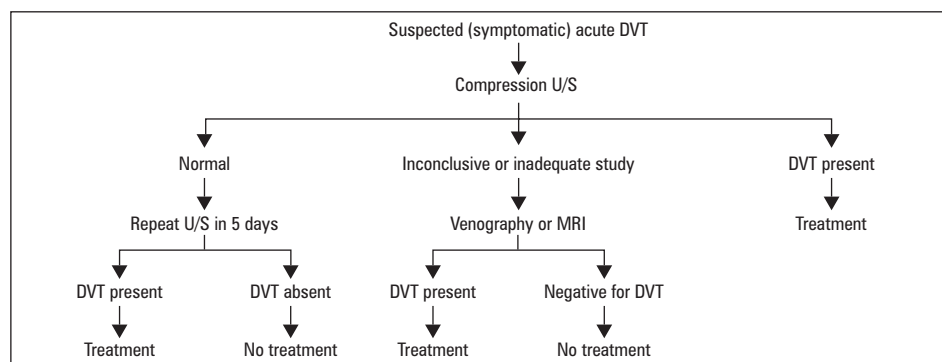


Figure 12. Approach to Suspected DVT

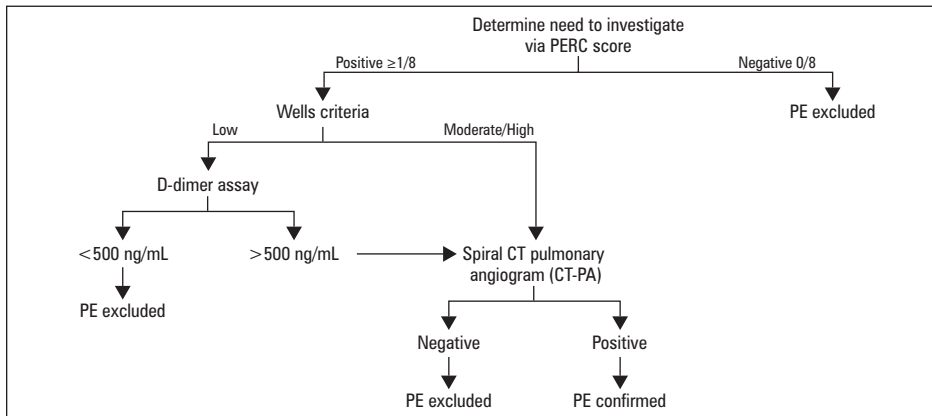


Figure 13. Approach to Suspected PE

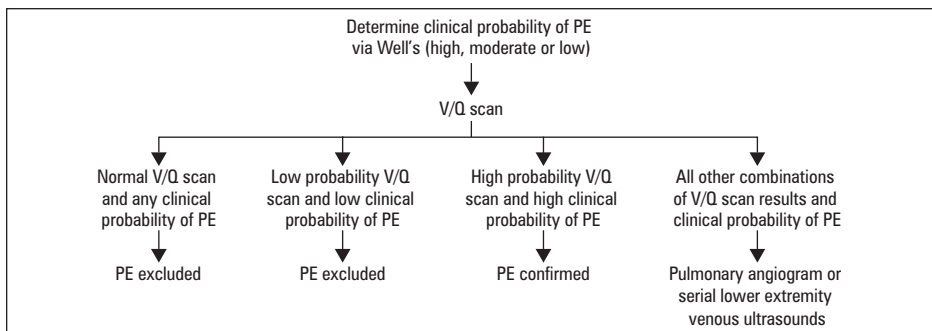


Figure 14. V/Q-Based Algorithm for Suspected PE

Clinical Criteria to Prevent Unnecessary Diagnostic Testing in Emergency Department Patients with Suspected Pulmonary Embolism

J Thromb Haemost 2004; 2(8):1247-55.
Purpose: To develop pulmonary embolism (PE) rule-out criteria (PERC) that can be used at the bedside, and prevents overtesting for PERC. Also, to prevent over-testing for PE, which includes the D-dimer test that frequently results in false positives.

Study: 21 variables were collected prospectively from 3148 ER patients evaluated for possible PE to develop rule-out criteria. The application of the developed rules was investigated in 1427 low-risk patients and 382 very-low risk patients.

Results: Eight variables were included in a block rule (Age <50 years, pulse <100 bpm, SaO₂ >94%, no unilateral leg swelling, no hemoptysis, no recent trauma or surgery, no prior PE or DVT, no hormone use) and a negative score was used to rule-out PE. In low-risk and very low-risk patients, the rule had a sensitivity of 96 and 100%, respectively and a specificity of 27 and 15%, respectively.

Summary: D-dimer testing for PE may not be favourable if all eight factors in the PERC are negative.

Diabetic Emergencies

- see also Endocrinology, E11

Diabetic Ketoacidosis (DKA)

- severe insulin deficiency resulting in hyperglycemia (11-55 mmol/L), dehydration and electrolyte abnormalities
- history and physical examination – often young, type 1 DM, may be first presentation of undiagnosed DM (may occur in small percentage of type 2 patients)
 - early symptoms: polyuria, polydipsia, malaise
 - late signs and symptoms
 - ♦ anorexia, nausea, vomiting, dyspnea (often due to acidosis), fatigue
 - ♦ abdominal pain
 - ♦ drowsiness, stupor, coma
 - ♦ Kussmaul's respiration
 - ♦ fruity acetone breath
- investigations
 - CBC, glucose, electrolytes, BUN/creatinine, Ca, Mg, phosphate, urine glucose and ketones
 - ABG
 - ECG (MI possible precipitant; electrolyte disturbances may predispose to arrhythmia)
- management
 - rehydration
 - ♦ bolus of NS, then high rate NS infusion (but beware of overhydration and cerebral edema, especially in pediatric patients)
 - potassium
 - ♦ essential to avoid hypokalemia: replace KCl (20 mEq/L if adequate renal function and initial K <5.5 mmol/L)
 - ♦ use cardiac monitoring if potassium levels normal or low
 - insulin
 - ♦ critical, as this is the only way to turn off gluconeogenesis/ketosis
 - ♦ do not give insulin if K <3.3 mmol/L
 - ♦ initial bolus of 5-10 U short-acting/regular insulin (or 0.2 U/kg) IV in adults (controversial – may just start with infusion)
 - ♦ followed by continuous infusion at 5-10 U (or 0.1 U/kg) per hour
 - ♦ add D5W when blood glucose <15 mM to prevent hypoglycemia
 - bicarbonate is not given unless patient is at risk of death or shock (typically pH <7.0)



Precipitating Factors in DKA

The 5 "I"s

Infection
 Ischemia
 Infarction
 Intoxication
 Insulin missed



4 criteria for DKA Dx: hyperglycemia, metabolic acidosis, hyperketonemia, ketonuria.

Hyperosmolar Hyperglycemic State (HHS)

- state of extreme hyperglycemia (44-133.2 mmol/L) due to relative insulin deficiency, increased counter-regulatory hormones, gluconeogenesis, and dehydration (due to osmotic diuresis) in type 2 DM, high mortality (approaches 50% even with optimal management)
- history and physical examination
 - mental disturbances, coma, delirium, seizures
 - polyuria
 - nausea, vomiting
- investigations
 - CBC, electrolytes, creatinine, BUN, glucose, Mg, phosphate, urine glucose and ketones
 - ABG
 - ECG
- management
 - rehydration with NS (total water deficit estimated at average 100 cc/kg body weight)
 - O₂ and cardiac monitoring, frequent electrolytes and glucose monitoring
 - insulin as required
 - identify and treat cause



Cerebral edema may occur if hyperosmolality treated too aggressively.

Hypoglycemia

- very common ED presentation
- management focus
 - treatment of hypoglycemia
 - investigation of cause (most often due to exogenous insulin, alcohol, sulfonylureas)
- history and physical examination
 - last meal, known diabetes, prior similar episodes, drug therapy and compliance
 - liver/renal/endocrine/neoplastic disease
 - depression, alcohol or drug use
- management
 - IV access and rapid BG
 - D50W 50 mL IV push, glucose PO if mental status permits
 - if IV access not possible, glucagon 1-2 mg IM, repeat x 1 in 10-20 min
 - O₂, cardiac, frequent BG monitoring
 - thiamine 100 mg IM
 - full meal as soon as mental status permits
 - if episode due to long acting insulin, or sulfonylureas, watch for prolonged hypoglycemia due to long t_{1/2} (may require admission for monitoring)
 - search for cause

**Drugs Inducing Hypoglycemia**

Insulin	Sulfa abx
Sulfonylureas	Cotrimazole
Ethanol	Ampicillin
Salicylates	Tetracycline
Acetaminophen	Amphetamines
NSAIDs	Cocaine
β-adrenergic agonists	Pyridoxine
Lithium	ACE-I
Calcium	Theophylline
MAOI	Quinine
Coumadin	

Electrolyte Disturbances

- see [Nephrology](#) and [Endocrinology](#)

Table 15. Electrolyte Disturbances

Electrolyte Disturbance	Common Causes	Symptoms	Treatment	Special Considerations
Hypernatremia	Inadequate H ₂ O intake (elderly/disabled) or inappropriate excretion of H ₂ O (diuretics, Li, DI)	Lethargy, weakness, irritability, and edema. Seizures and coma occur with severe elevations of Na levels (>158 mmol/L)	Salt restrict and give free water	No more than 12 mmol/L in 24 hrs drop in Na (0.5 mmol/L/hr) due to risk of cerebral edema, seizures, death
Hyponatremia	Hypo-osmolar (dilutional e.g. CHF, cirrhosis, ascites) and hyper-osmolar (usually glucose)	Acute: Neurologic symptoms 2° to cerebral edema, h/a, decreased LOC, depressed reflexes	Water restrict Acute: correct rapidly 3% NaCl 1-2 cc/kg/h Chronic: IV NS + furosemide	Limit total rise to 8 mmol/L in 24 hrs (0.5 mmol/L/hr maximum) as patients are at risk of central pontine myelinolysis
Hyperkalemia	Rhabdomyolysis, insulin deficiency, metabolic acidosis	Nausea, palpitations, muscle stiffness, areflexia	Protect heart: Ca gluconate Shift K into cells: Insulin R, NaHCO ₃ , Ventolin	ECG: Peaked/Narrow T wave, decreased P wave, prolonged PR interval, widening of QRS, AV block, V fib
Hypokalemia	Metabolic alkalosis, insulin, diuretics, anorexia Ventolin	Nausea, vomiting, fatigue, muscle cramps, constipation	K-Dur®, K sparing diuretics, IV solutions with 20-40 mEq KCl per liter over 3-4 hours	ECG: U waves most important, flattened/inverted T waves, prolonged QT, depressed ST May need to restore Mg
Hypercalcemia	Hyper-PTH and malignancy account for approx. 90% of cases	Multisystem including CVS, GI (groans), renal (stones), rheumatological, MSK (bones), psychiatric (moans)	Isotonic saline + lasix if hypervolemic Bisphosphonates, dialysis, chelation (EDTA or oral phosphate)	Patients with more severe or symptomatic hypercalcemia are usually dehydrated and require saline hydration as initial therapy
Hypocalcemia	Iatrogenic, low Mg, liver dysfunction, 1° hypo-PTH	Laryngospasm, hyperreflexia, parasthesia, tetany, Chvostek's and Trousseau's sign	Acute (ionized Ca <0.7 mM) requires immediate treatment: IV calcium gluconate 1-2 g in 10-20 mins followed by slow infusion	Prolonged QT interval can arise leading to arrhythmia as can upper airway obstruction

Hypertensive Emergencies

Hypertensive Emergency (Hypertensive Crisis)

- definition: acute elevation of systolic and diastolic BP (sBP >200, dBP >120) and associated acute end-organ damage (CNS, renal, CVS, haem, pregnancy related)
 - hypertensive encephalopathy: cerebral hyperperfusion due to blood pressure in excess of the capacity for cerebral autoregulation
 - signs and symptoms: headache, nausea, vomiting, mental status changes (lethargy to coma), fundoscopic changes, over hours can lead to coma and death
 - acute renal failure: can be either the cause or effect of a hypertensive emergency
 - diagnosis: proteinuria, RBCs and RBC casts in urine, elevated BUN and creatinine
 - treatment: IV calcium channel blockers, \pm emergent ultrafiltration
 - cardiovascular: MI, CHF, thoracic aortic dissection
 - left ventricular failure (LVF): decreased LV function due to increased afterload, increased oxygen demand and decreased coronary blood flow
 - signs and symptoms: chest pain, SOB
 - treatment: avoid diazoxide, hydralazine, minoxidil as these drugs increase oxygen demand
 - thoracic aortic dissection (see Cardiology, C48)

Pregnancy Induced Hypertension (PIH) see Obstetrics, OB14

- watch for HTN, abdominal pain with severe nausea and vomiting, seizures, proteinuria, thrombocytopenia, increased AST, clonus, and hyper-reflexia
 - initial treatment: lower BP, check reflexes, consider MgSO_4 if at risk for developing eclampsia, and assess risk to mother and fetus (e.g. deliver)
 - antihypertensives: hydralazine 5mg doses in 15 min intervals when dBP >105 or sBP >160, until dBP 90-100; consider IV labetalol as an alternative

Catecholamine-Induced Hypertensive Emergencies

- etiology: discontinuation of short-acting sympathetic blocker (e.g. clonidine, propranolol), pheochromocytoma, sympathomimetic drugs (cocaine, amphetamines, phencyclidine), MAOI in combination with sympathomimetics or tyramine-containing foods (cheese, red wine)
- treatment: immediate goal of IV therapy is to reduce the mean arterial pressure (MAP) by 25% in 30-60 min (5-10 min for aortic dissection) then a gradual reduction in MAP over the next 6 hrs to 160/100
 - BP should NOT be lowered rapidly in patients with major cerebrovascular event
 - decreasing BP too fast may extend or worsen stroke
 - if dBP >120, aim to reduce dBP by 20% in the first 24 hrs
 - treatment may be initiated in the ED followed by prompt admission to ICU for continuous BP monitoring
 - re-administer sympathetic blocker if due to withdrawal (e.g. clonidine, propranolol)

Hypertensive Urgency

- definition: severely elevated blood pressure (usually sBP >180, dBP >115) with no evidence of end-organ damage
- most commonly due to non-adherence with medications
- treatment: gradually reduce pressure over 24-48 hours to a level appropriate for the patient
- goal is to differentiate hypertensive emergencies from hypertensive urgencies

History and Physical Examination

- prior hypertensive crises
- antihypertensive medications prescribed, adherence, and BP control
- MAOIs, substance use, use of stimulants or withdrawal from sedatives including EtOH
- blood pressure measurement in all limbs
- fundoscopic exam (hemorrhages, papilledema, etc.), gross motor examination

Investigations

- CBC, electrolytes, BUN, creatinine, urinalysis
- peripheral blood smear – to detect microangiopathic hemolytic anemia
- CXR – if SOB or chest pain
- ECG, troponins, CK – if chest pain
- CT head – if neurological findings or severe headache

Treatment of Hypertensive Emergencies

- see Table 16



Signs of Fluid Depletion

Increased heart rate
Postural changes in vital signs
Decreased urine output (normal: 0.5 cc/kg/hr)
Hypertensive
Decreased skin turgor
Sunken eyes
Dry mucous membranes
Decreased capillary refill



HELLP Syndrome (seen only in preeclampsia/eclampsia)
Hemolytic anemia
Elevated Liver enzymes
Low Platelet count



Catecholamine Induced Hypertensive Emergencies

Avoid use of non-selective β -blockers as they inhibit β -mediated vasodilation and leave α -adrenergic vasoconstriction unopposed.



Signs/Symptoms of CNS Hypertensive Emergency

N/V
Seizure
Headache or altered mental status
Cushing response



Evidence of End-Organ Damage

CNS: headache, focal neurological signs, seizures
CVS: angina, CHF, back pain (aortic dissection)
Renal: hematuria, oliguria
Eyes: papilledema, retinal hemorrhages



With CNS manifestations of severe hypertension, it is often difficult to differentiate causal relationships [i.e. hypertension could be secondary to primary cerebral event (Cushing effect)].



Most commonly used agents for hypertensive crisis are labetalol and nitroprusside.



Drugs that Increase Adrenergic Stimulation
MAOIs
TCAs
Amphetamines
Cocaine

Table 16. Most Commonly Used Agents for the Treatment of Hypertensive Crisis

Drug	Dosage	Onset of Action	Duration of Action	Adverse Effects*	Special Indications
VASODILATORS					
Sodium Nitroprusside (vascular smooth muscle dilator) 1st line	0.25-10 µg/kg/min	Immediate	3-5 min	N/V, muscle twitching, sweating, cyanide intoxication, coronary steal syndrome	Most hypertensive emergencies (esp CHF, aortic dissection) Use in combination with β-blockers (e.g. esmolol) in aortic dissection Caution with high ICP and azotemia
Nicardipine (CCB)	2 mg IV bolus, then 4 mg/kg/hr IV	15-30 min	40 min	Tachycardia, headache, flushing, local phlebitis (e.g. encephalopathy, RF, eclampsia, sympathetic crisis)	Most hypertensive emergencies Caution with acute CHF
Fenoldopam Mesylate (dopamine receptor antagonist)	0.05-0.1 µmg/kg/min IV	<5 min	8-10 min	Tachycardia, headache, nausea, flushing (e.g. acute RF)	Most hypertensive emergencies Caution with glaucoma
Enalapril (ACEI)	0.625-1.25 mg IV q6h	15-30 min	12-24 hr	Theoretical fall in pressure in high renin states not seen in studies	Acute LV failure Avoid in acute MI, pregnancy, acute RF
Nitroglycerin	5-20 µg/min IV	1-2 min	3-5 min	Hypotension, bradycardia, headache, lightheadedness, dizziness	MI/Pulmonary edema
Hydralazine	5-10 mg IV/IM q20min (max 20 mg)	5-20 min	2-6 hrs	Dizziness, drowsiness, headache, tachycardia, Na retention	Eclampsia
ADRENERGIC INHIBITORS					
Labetalol	20 mg IV bolus q10 min or 0.5-2 mg/min	5-10 min	3-6 hr	Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies (esp. eclampsia) Avoid in acute CHF, HB > 1st degree
Esmolol	250-500 µg/kg/min 1 min, then 50 µg/kg/min for 4 min; repeat	1-2 min	10-20 min	Hypotension, nausea, bronchospasm	Aortic dissection, acute MI SVT dysrhythmias, perioperative HTN Avoid in acute CHF, HB > 1st degree
Phentolamine	5-15 mg q5-15 min	1-2 min	3-10 min	Tachycardia, headache, flushing	Catecholamine excess (e.g. pheo)

*Hypotension may occur with all of these agents



If patient presents within 4.5 hours of onset of disabling neurological deficits greater than 60 minutes with no signs of resolution, they may be candidate for thrombolysis. Do brief assessment and order stat CT head.

Exclusion Criteria for tPA:

Suspected subarachnoid hemorrhage
Previous intracranial hemorrhage
Cerebral infarct or severe head injury within the past 3 months
Recent pericarditis
Major surgery within the past 14 days
GI or urinary hemorrhage within the past 21 days
Recent lumbar puncture or arterial puncture at noncompressible site
Patient is pregnant
BP = 185 mmHg systolic, or = 110 mmHg diastolic
Bleeding diathesis
Prolonged PTT (more than 40 seconds) or INR > 1.4
Platelet count < 100,000
Blood glucose < 2.8 or > 22 mmol/L
Intracranial hemorrhage on CT/or large volume infarct
Seizure at onset causing deficit
Previously ADL dependent (clinical judgment)

Stroke

- see Neurology, N44
- can be ischemic (80% of all strokes) or hemorrhagic

History

- consider acute stroke if acute neurological deficit (focal or global) or altered LOC
- more likely to be hemorrhagic if: nausea, vomiting, headache, change in LOC, seizure
- common symptoms of stroke: abrupt onset of hemiparesis/monoparesis, visual loss/field deficits, diplopia, dysarthria, ataxia, vertigo, aphasia, sudden decrease in LOC
- determine time of symptom onset for consideration of thrombolytic therapy
- DDx includes hypoglycemia, Todds paralysis, peripheral nerve injury, Bell's palsy, tumour

Physical Examination

- vitals
- if decreased LOC: assess for ability to protect airway
- rule out trauma, infection, meningeal irritation
- search for cardiovascular causes of stroke
 - ocular fundi (retinopathy, emboli, hemorrhage) and pupils
 - CVS (murmurs, gallops, AFib)
 - PVS (auscultate for carotid bruits)



- neuro
 - mental status, LOC, cranial nerves, motor function, sensory function, cerebellar function, gait, deep tendon reflexes
 - confirm presence of stroke syndrome, and distinguish from stroke mimics (seizure, systemic infection, brain tumour, positional vertigo, Bell's palsy)
 - establish neurological baseline should patient improve/deteriorate

Table 17. Stroke Syndromes

Region of Stroke	Stroke Syndrome
Anterior Cerebral Artery	Primarily frontal lobe function affected Altered mental status, impaired judgment, contralateral lower extremity weakness and hypoesthesia, gait apraxia
Middle Cerebral Artery	Contralateral hemiparesis (arm and face weakness > leg weakness) and hypoesthesia, ipsilateral hemianopsia, gaze preference to side of lesion ± agnosia, receptive/expressive aphasia
Posterior Cerebral Artery	Affects vision and thought Homonymous hemianopsia, cortical blindness, visual agnosia, altered mental status, impaired memory
Vertebrobasilar Artery	Wide variety of CN, cerebellar and brainstem deficits: vertigo, nystagmus, diplopia, visual field deficits, dysphagia, dysarthria, facial hypoesthesia, syncope, ataxia Loss of pain and temperature sensation ipsilateral face and contralateral body

Investigations

- CBC, electrolytes, blood glucose, coagulation studies, ± cardiac biomarkers, ± toxicology screen
- non-contrast CT head: look for hemorrhage, ischemia
- ECG ± echocardiogram: rule out atrial fibrillation, acute MI as source of emboli
 - other imaging: carotid dopplers, CTA, MRA as appropriate

Management

- quickly determine if patient is eligible for thrombolysis (need acute onset less than 4.5 hours from drug administration time AND compatible physical findings AND normal CT with no bleed) – not much time to do all of this (often requires designated stroke team)
- ABCs with RSI if GCS ≤8, rapidly decreasing GCS, or inadequate airway protection reflexes
- IV ± cardiac monitoring
 - judge fluid rate carefully to avoid overhydration (cerebral edema) as well as underhydration (underperfusion of the ischemic penumbra)
- BP control: only treat severe hypertension (sBP >200, dBP >120, mean arterial BP >140) or hypertension associated with hemorrhagic stroke transformation, cardiac ischemia, aortic dissection, or renal damage; use IV nitroprusside or labetalol
- cerebral edema control: hyperventilation, mannitol to decrease ICP if necessary
- consult neurosurgery, neurology as indicated

Medications

- acute ischemic stroke: thrombolytics (rt-PA, e.g. alteplase) if within 3 hours of symptom onset with no evidence of hemorrhage on CT scan
- antiplatelet agents: prevent recurrent stroke or stroke after TIAs, e.g. aspirin (1st-line); clopidogrel, ticlopidine (2nd-line)

**Differentiation of UMN Disease versus LMN Disease**

Category	UMN Disease	LMN Disease
Muscular deficit	Muscle groups	Individual muscles
Reflexes	Increased	Decreased/absent
Tone	Increased	Decreased
Fasciculations	Absent	Present
Atrophy	Absent/minimal	Present

**7 Causes of Emboli from the Heart**

Atrial Fib
MI
Endocarditis
Valvular disease
Dilated cardiomyopathy
Left heart myxoma
Prosthetic Valves

**Causes of Acute Ataxia****UNABLE TO STAND**

Underlying weakness (mimic ataxia)
Nutritional neuropathy (vitamin B₁₂ deficiency)
Arteritis/vasculitis
Basilar migraine
Labyrinthitis/vestibular neuronitis
Encephalitis/infection

Trauma (post-concussive)
Other (rare genetic or metabolic disease)

Stroke (ischemia or hemorrhage)
Toxins (drugs, toluene, mercury)
Alcohol
Neoplasm/paraneoplastic syndrome
Demyelination (Miller Fisher, Guillain Barré, MS)

Gynecologic/Urologic Emergencies

Vaginal Bleed

- see Gynecology, GY6 and Obstetrics, OB20

Etiology

- pregnant patient
 - 1st/2nd trimester pregnancy: ectopic pregnancy, abortion (threatened, incomplete, complete, missed, inevitable, septic), molar pregnancy
 - 2nd/3rd trimester pregnancy: placenta previa, placental abruption, premature rupture of membranes, preterm labour
 - either: trauma, bleeding cervical polyp
- postpartum
 - postpartum hemorrhage, uterine inversion, retained placental tissue, endometritis
- non-pregnant patients
 - dysfunctional uterine bleeding, uterine fibroids, pelvic tumours, trauma, endometriosis, PID, exogenous hormones



Vaginal bleeding can be life threatening. Always start with ABCs and ensure your patient is stable.

History

- menstrual history, sexual activity, contraception, history of PID
- pregnancy details
- determine amount of blood
- urinary, GI symptoms

Physical Examination

- look for signs of hypovolemia
- pelvic examination – NOT if suspected placenta previa (ultrasound first)
- speculum exam
 - if pregnant use sterile speculum
- bimanual examination
 - if pregnant use sterile gloves
 - if patient is near term with possible rupture of membranes and without other indications defer bimanual examination (infection risk)

Investigations

- β -hCG test for all patients with child-bearing potential
- CBC, blood and Rh type, quantitative β -hCG, PTT, INR
- type and cross if significant blood loss
- 1st/2nd trimester/non-pregnant
 - ultrasound (U/S) – intrauterine pregnancy, ectopic pregnancy, traumatic injury, foreign body
 - must correlate U/S findings with β -hCG if U/S is non-diagnostic (transvaginal ultrasound will not see gestation in uterus if β -hCG <1200 – must repeat)
- 2nd/3rd trimester pregnancy
 - U/S if no fetal heart tones, no documented intrauterine pregnancy or unknown lie of placenta
 - non-stress test to assess fetal well-being during work up of mother
 - DIC panel if placental abruption – CBC, PTT, INR, fibrinogen
- postpartum
 - U/S for retained products
 - β -hCG if concerned about retained tissue

Management

- ABCs
- pulse oximeter and cardiac monitors if unstable
- Rh immune globulin for vaginal bleeding in pregnancy and Rh-negative mother
- 1st/2nd trimester pregnancy
 - ectopic pregnancy: definitive treatment with surgery or methotrexate
 - intrauterine pregnancy, no concerns of coexistent ectopic: discharge patient with obstetrics follow-up
 - U/S indeterminate or β -hCG >1000-2000 IU: further work-up and/or gynecology consult
 - abortions: if complete, discharge if stable; for all others, acquire gynecology consult
- 2nd/3rd trimester pregnancy
 - placenta previa or placental abruption: obstetrics consult for possible admission
- postpartum
 - uterine inversion: replace uterus immediately, may require operative management
 - postpartum hemorrhage: extraction of placenta if retained, hysterectomy if uncontrolled bleeding
 - retained tissue: D&C
 - endometritis: IV antibiotics
- non-pregnant
 - dysfunctional uterine bleeding (prolonged or heavy flow \pm breakthrough bleeding and without ovulation, a diagnosis of exclusion)
 - ♦ <35-40 years of age: Provera® 10 mg PO x 10 days, warn patient of a withdrawal bleed, discharge if stable
 - ♦ if unstable, admit for IV hormonal therapy, possible D&C
 - ♦ >35-40 years of age: uterine sampling necessary prior to initiation of hormonal treatment to rule out endometrial cancer, U/S for any masses felt on exam
 - structural abnormalities: fibroids or uterine tumours may require excision for diagnosis/treatment, U/S for workup of other pelvic masses, Pap smear/biopsy for cervical lesions

Disposition

- the decision to admit or discharge should be based on the stability of the patient, as well as the nature of the underlying cause; consult gynecology for admitted patients
- if patient can be safely discharged, ensure follow up with family physician or gynecologist
 - instruct patient to return to emergency for increased bleeding, presyncope



Need β -hCG ≥ 1200 to see interuterine changes on transvaginal U/S.



Classifying miscarriage (abortion):

Missed – non-viable intrauterine pregnancy
Threatened – viable intrauterine pregnancy with os closed
Inevitable – os closed, no products of conception passed
Incomplete – products of conception partially expelled
Complete – products of conception completely expelled
Septic – any of above with presence of infection (usually incomplete)
Recurrent – >3 spontaneous abortions (recurrent pregnancy loss)



Vaginal bleeding (and its underlying causes) can be a very emotionally taxing presentation for patients. Ensure appropriate support is provided.

Pregnant Patient in the ER

Table 18. Complications of Pregnancy

Trimester	Fetal	Maternal
First 1-14 wks	Pregnancy failure • Spontaneous abortion • Fetal demise • Gestational trophoblastic disease	Ectopic pregnancy Anemia Hyperemesis gravidarum UTI/pyelonephritis
Second 15-27 wks	Disorders of fetal growth • IUGR • Oligo/polyhydramnios	Gestational diabetes mellitus Rh incompatibility UTI/pyelonephritis
Third 28-40 wks	Vasa previa	Preterm labour/PPROM Preeclampsia/eclampsia Placenta previa Placental abruption Uterine rupture DVT

Nephrolithiasis (Renal Colic)

- see Urology, U15

Epidemiology and Risk Factors

- 10% of population (twice as common in males)
- recurrence 50% at 5 yrs
- peak incidence 30-50 years of age
- 75% of stones <5 mm pass spontaneously within 2 weeks, larger stones may require consultation

Clinical Features

- urinary obstruction → upstream distention of ureter or collecting system → severe colicky pain
- may complain of pain at flank, groin, testes, or tip of penis
- writhing, never comfortable, nausea, vomiting, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency)
- fever, chills, rigors in secondary pyelonephritis

Differential Diagnosis of Renal Colic

- acute ureteric obstruction (other causes)
 - UPJ obstruction
 - sloughed papillae
 - clot colic from gross hematuria
 - extrinsic (e.g. tumour)
- acute abdomen – biliary, bowel, pancreas, AAA
- gynecological – ectopic pregnancy, torsion/rupture of ovarian cyst
- pyelonephritis (fever, chills, pyuria, vomiting)
- radiculitis (L1) – herpes zoster, nerve root compression

Investigations

- screening labs
 - CBC → elevated WBC in presence of fever suggests infection
 - electrolytes, Cr, BUN → to assess renal function
 - urinalysis: R&M (WBCs, RBCs, crystals), C&S
- imaging
 - non-contrast spiral CT is the study of choice
 - abdominal ultrasound may demonstrate stone or hydronephrosis
- strain all urine → stone analysis

Management

- analgesics, antiemetics, IV fluids
- urology consult may be indicated, especially if stone >5 mm, or if patient has signs of obstruction or infection
- α-blocker helpful to increase stone passage in select cases

Disposition

- most patients can be discharged
- ensure patient is stable, has adequate analgesia, and is able to tolerate oral medications
- may advise hydration, calcium supplementation, and limitation of protein, sodium, oxalate and alcohol intake



Kidney Stones
 80% Ca
 10% Struvite
 10% Uric acid



Indications for Admission to Hospital

- Intractable pain
- Fever (suggests infection)
- Single kidney with ureteral obstruction
- Bilateral obstructing stones
- Intractable vomiting
- Compromised renal function

Ophthalmologic Emergencies

Ophthalmologic Foreign Body and Corneal Abrasion

- see also [Ophthalmology](#), OP17



ALWAYS assess visual acuity in both eyes when a patient presents to the ER with an ophthalmologic complaint.



Any etiology of red eyes may also present with blurred vision.



Other Ophthalmologic Emergencies
(See [Ophthalmology](#), OP5)

Infectious – Red eye (Table 19), endophthalmitis, orbital cellulitis
Trauma – retinal detachment, globe rupture, orbital blow-out fractures, chemical burns
Autoimmune – Giant cell arteritis



Contraindications to Pupil Dilation

- Shallow anterior chamber
- Iris-supported lens implant
- Potential neurological abnormality requiring pupillary evaluation
- Caution with CV disease – mydriatics can cause tachycardia

History

- patient may complain of pain, tearing, itching, redness, photophobia, foreign body sensation
- elicit history of potential trauma to eye
- mechanism of foreign body insertion – if high velocity injury suspected (welding, metal grinding, metal striking metal), must obtain orbital x-rays or ultrasound to exclude presence of intraocular metallic foreign body
- see Table 19 for important considerations of red eye in the emergency department

Table 19. Differential Diagnosis of Red Eye in the Emergency Department

Symptom	Possible Serious Etiology
Light Sensitivity	Iritis, keratitis, abrasion, ulcer
Unilateral	Above + herpes simplex, acute angle closure glaucoma
Significant pain	Above + scleritis
White spot on cornea	Corneal ulcer
Blurred vision	All of the above
Non-reactive pupil	Acute glaucoma, iritis
Copious discharge	Gonococcal conjunctivitis

Physical Examination

- visual acuity in both eyes with best corrected vision
- pupils, extraocular movement, external ocular structures
- fundoscopy
- tonometry – measurement of intraocular pressure (with Tonopen)
 - normal pressure: 10-20 mmHg, glaucoma associated with increased pressures
- slit lamp exam:
 - start with unaffected eye, perform a systematic examination: lids, lashes, lacrimal apparatus, conjunctiva, sclera, cornea, anterior chamber, iris, lens, vitreous
 - proparacaine anaesthetic drops may ease examination
 - look for rust ring with metallic foreign body, corneal edema, anterior chamber cells/flare
 - may use fluorescein dye which stains de-epithelialized cornea green when viewing with cobalt blue filter

Management

- copious irrigation with saline for any foreign body
- remove foreign body under slit lamp exam with cotton swab or sterile needle
- antibiotic drops qid until healed
- patching may not improve healing or comfort – do not patch contact lens wearers
- limit use of topical anesthetic to examination only
- consider tetanus prophylaxis
- ophthalmology consult if globe penetration suspected

Initial Management of other Ophthalmologic Emergencies

- ruptured globe – stabilize any foreign body, shield eye with no pressure, elevate head of bed to 30°, tetanus prophylaxis, IV antibiotics, NPO, analgesic, antiemetic, sedation prn
- retinal artery occlusion – globe massage, paper bag breathing, carbogen inhalation (95% oxygen, 5% carbon dioxide)
- chemical burn – immediate copious irrigation, may consider topical anaesthetic drops to facilitate irrigation
- acute angle-closure glaucoma – IV or PO acetazolamide, topical pilocarpine and timolol
- preseptal cellulitis (2° to superficial trauma) – topical or systemic Abx
- orbital cellulitis (2° to sinusitis) – admit, IV antibiotics, blood cultures, CT

Disposition

- most patients can be discharged with outpatient ophthalmology follow-up
- admit patients requiring emergent ophthalmologic procedures or IV antibiotics

Dermatologic Emergencies

Life Threatening Dermatoses

Rash Characteristics

- **DIFFUSE RASH**
 - **staphylococcal scalded skin syndrome (SSSS)**
 - ♦ caused by an exotoxin from infecting strain of coagulase-positive *S. aureus*
 - ♦ mostly occurs in children
 - ♦ prodrome: fever, irritability, malaise and skin tenderness
 - ♦ sudden onset of diffuse erythema: skin is red, warm, and very tender
 - ♦ flaccid bullae that are difficult to see, then desquamate in large sheets
 - ♦ Nikolsky's sign: gentle lateral stroking of skin causes epidermis to separate
 - **toxic epidermal necrolysis (TEN)**
 - ♦ see Dermatology, D22
 - ♦ caused by drugs (e.g. phenytoin, sulfas, penicillins and NSAIDs), bone marrow transplantation, blood product transfusions
 - ♦ usually occurs in adults
 - ♦ diffuse erythema followed by necrosis
 - ♦ severe mucous membrane blistering
 - ♦ entire epidermis desquamation
 - ♦ high mortality (>50%)
 - **toxic shock syndrome (TSS)**
 - ♦ see Infectious Diseases, ID27
 - ♦ caused by superantigen from *S. aureus* or GAS activating T-cell and cytokines
 - ♦ patient often presents with onset of shock and multi-organ failure, fever
 - ♦ diffuse erythematous macular rash
 - ♦ at least 3 organ systems involved: CNS, respiratory, GI, muscular, mucous membranes, renal, liver, hematologic, skin (necrotizing fasciitis, gangrene)
- **VESICOBULLOUS LESIONS**
 - **erythema multiforme (EM)**
 - ♦ see Dermatology, D22
 - ♦ immunologic reaction to herpes simplex
 - ♦ viral prodrome 1-14 days before rash
 - ♦ "target lesion": central gray bulla or wheal surrounded by concentric rings of erythema and normal skin
 - **Stevens-Johnson syndrome (SJS)**
 - ♦ see Dermatology, D22
 - ♦ related to drugs such as antiepileptics and biologic agents, e.g. infliximab
 - ♦ EM with constitutional symptoms and mucous membrane involvement (milder mucous membrane involvement than TEN)
- **DISCRETE LESIONS**
 - **pyoderma gangrenosum**
 - ♦ often associated with immunocompromised patients (HIV, leukemia or lymphoma) with Gram-negative sepsis
 - ♦ often occurs in arms, hands, feet, or perineal region
 - ♦ usually begins as painless macule/vesicle → pustule/bulla on red/blue base → sloughing, leaving a gangrenous ulcer
 - **disseminated gonococcal infection (DGI)**
 - ♦ see Dermatology, D32
 - ♦ fever, skin lesions (pustules/vesicles on erythematous base ~5 mm in diameter), arthritis (joint swelling and tenderness), septic arthritis (in larger joints, e.g. knees, ankles and elbows)
 - ♦ most commonly in gonococcus positive women during menstruation or pregnancy
 - ♦ skin lesions usually appear in extremities and resolve quickly (<7 days)
 - **meningococcemia**
 - ♦ flu-like symptoms of headache, myalgia, nausea and vomiting
 - ♦ petechial, macular or maculopapular lesions with gray vesicular centres
 - ♦ usually a few millimeters in size but may become confluent and hemorrhagic
 - ♦ usually appear in extremities but may appear anywhere
 - ♦ look for signs of meningeal irritation: Brudzinski, Kernig, nuchal rigidity, jolt accentuation

History and Physical Examination

- determine onset, course, location of skin lesions
- fever, joint pain
- associated symptoms: CNS, resp, GU, GI, renal, liver, mucous membranes
- medication history
- vitals



Thorough dermatologic examinations are required; examination of asymptomatic skin may identify more lesions! Ensure adequate draping during dermatologic examinations.

Investigations

- immediate consultation if patient unstable
- CBC, electrolytes, creatinine, AST, ALT, ALP, blood culture, skin biopsy, serum immunoglobulin levels (serum IgE)

Management

- general: judicious IV fluids and electrolyte control, consider vasopressors if hypotensive, prevention of infection
- determine if admission and consult needed: dermatology or infectious diseases
- specific management is determined by etiology
 - SSSS, TSS, DGI and meningococemia
 - ♦ IV antibiotics
 - EM, SJS, and TEN
 - ♦ stop precipitating medication
 - ♦ fluids
 - ♦ symptomatic treatment: antihistamines, antacids, topical corticosteroids, systemic corticosteroids (controversial), prophylactic oral acyclovir, consider IVIG
 - ♦ TEN: debride necrotic tissue

Disposition

- most cases will require urgent care and hospitalization
- TEN: early transfer to burn centre improves outcome

Environmental Injuries



Heat Exhaustion and Heat Stroke

- predisposing factors: young persons who overexert themselves, older adults who cannot dissipate heat at rest (e.g. using anticholinergic drugs such as antihistamines or TCAs), and patients with schizophrenia who are using anticholinergic or neuroleptic medications

Heat Exhaustion (HE)

- clinical features relate to loss of circulating volume caused by exposure to heat stress
- “water depletion”: HE occurs if lost fluid not adequately replaced
- “salt depletion”: HE occurs when losses replaced with hypotonic fluid

Heat Stroke

- life-threatening emergency resulting from failure of normal compensatory heat-shedding mechanisms
- divided into classical and exertional subtypes (see Table 20)
- if patient does not respond relatively quickly to cooling treatments, consider other possible etiologies of hyperpyrexia (e.g. meningitis, thyroid storm, anticholinergic poisoning, delirium tremens, other infections)

Table 20. Heat Exhaustion vs. Heat Stroke

	Heat Exhaustion	Classical Heat Stroke	Exertional Heat Stroke
Clinical Features	<ul style="list-style-type: none"> • Non-specific malaise, headache, fatigue • Body temp <40.5°C (usually normal) • No coma or seizures • Dehydration (↑ HR, orthostatic hypotension) 	<ul style="list-style-type: none"> • Occurs in setting of high ambient temperatures (e.g. heat wave, poor ventilation) • Often patients are older, poor, and sedentary or immobile • Dry, hot skin • Temp usually >40.5°C • Altered mental status, seizures, delirium, coma • May have elevated AST, ALT 	<ul style="list-style-type: none"> • Occurs with high endogenous heat production (e.g. exercise) and overwhelmed homeostatic mechanisms • Patients often younger, more active • Skin often diaphoretic • Other features as for classical HS, but may also have DIC, acute renal failure, rhabdomyolysis, marked lactic acidosis
Treatment	<ul style="list-style-type: none"> • Rest in a cool environment • Normal saline IV if orthostatic hypotension; otherwise replace losses slowly PO 	<ul style="list-style-type: none"> • Cool down body temperature with water mist (e.g. spray bottle) and standing fans • Ice water immersion also effective; monitor body temp closely to avoid hypothermic overshoot • Secure airway because of risk of seizures and aspiration • Give fluid resuscitation if still hypotensive after above therapy • Avoid α-agonists (e.g. epinephrine) peripheral vasoconstriction and antipyretics (e.g. ASA) 	



Heat exhaustion (HE) may closely resemble heat stroke. HE may eventually progress to heat stroke. Therefore if diagnosis is uncertain treat as heat stroke.

Hypothermia and Cold Injuries



- predisposing factors: extremes of age, lack of housing, drug overdose, EtOH ingestion, trauma (incapacitating), cold water immersion, outdoor sports
- treatment based on: (a) re-warming and (b) supporting cardiorespiratory function
- complications: coagulopathy, acidosis, ventricular arrhythmias (VFib), asystole, volume and electrolyte depletion
- labs: CBC, electrolytes, ABG, serum glucose, creatinine/BUN, Mg, Ca, amylase, coagulation profile
- imaging: CXR (aspiration pneumonia, pulmonary edema are common)
- monitors: ECG, rectal thermistor, Foley catheter, NG tube, monitor metabolic status frequently

Table 21. Classification of Hypothermia

Class	Temp	Symptoms/Signs
Mild	32-34.9°C	Tachypnea, tachycardia, ataxia, dysarthria, shivering
Moderate	28-31.9°C	Loss of shivering, arrhythmias, Osborne (J) waves on ECG, decreased LOC, combative behaviour, muscle rigidity, dilated pupils
Severe	<28°C	Coma, hypotension, acidemia, ventricular fibrillation, asystole, flaccidity, apnea

Re-warming Options

- gentle fluid and electrolyte replacement in all (due to cold diuresis)
- Passive External Re-warming (PER)
 - suitable for most stable patients with core temperature >32.2°C
 - involves covering patient with insulating blanket; body generates heat and re-warms through metabolic process, shivering
- Active External Re-warming (AER)
 - involves use of warming blankets
 - beware “afterdrop” phenomenon (warming of extremities causes vasodilation and movement of cool pooled blood from extremities to core, resulting in a drop in core temperature → cardiac arrest)
 - safer when done in conjunction with active core re-warming
- Active Core Re-warming (ACR)
 - generally for patients with core temperature <32.2°C, and/or with cardiovascular instability
 - avoids “afterdrop” seen with AER alone
 - re-warm core by using
 - ♦ warmed humidified oxygen, IV fluids
 - ♦ peritoneal dialysis with warm fluids
 - ♦ gastric/colonic/pleural irrigation with warm fluids
 - ♦ external circulation (cardiopulmonary bypass machine) is most effective, fastest

Cardiac Arrest in the Hypothermic Patient

- do all procedures gently or may precipitate VFib
- check pulse and rhythm for at least 1 minute; may have profound bradycardia
- if any pulse at all (even very slow) do NOT do CPR
- if in VFib try to defibrillate up to max 3 shocks if core temperature <30°C
- intubate gently if required, ventilate with warmed, humidified O₂
- medications (vasopressors, antiarrhythmics) may not be effective at low temperatures
 - controversial; may try one dose
- focus of treatment is re-warming

FROSTBITE

Classification

- ice crystals form between cells
- classified according to depth – similar to burns (1st to 3rd degree)
- **1st degree**
 - symptoms: initial paresthesia, pruritus
 - signs: erythema, edema, hyperemia, no blisters
- **2nd degree**
 - symptoms: numbness
 - signs: blistering (clear), erythema, edema
- **3rd degree**
 - symptoms: pain, burning, throbbing (on thawing); may be painless if severe
 - signs: hemorrhagic blisters, skin necrosis, edema, no movement

Management

- treat for hypothermia: O₂, IV fluids, maintenance of body warmth
- remove wet and constrictive clothing

**Burn causes:**

Thermal (flame, scald)
Chemical
Radiation (UV, medical/therapeutic)
Electrical

**High Risk Factors for Infection**

- Puncture wounds
- Crush injuries
- Wounds greater than 12 hours old
- Hand or foot wounds, wounds near joints
- Immunocompromised patient
- Patient age greater than 50 years
- Prosthetic joints or valves (risk of endocarditis)



Use palm of the patient's hand to estimate 1% of BSA affected.

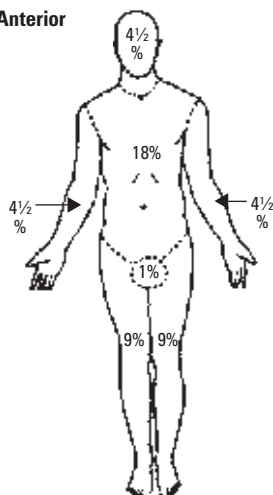
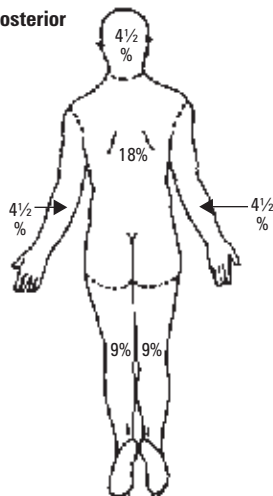
Anterior**Posterior**

Figure 15. Rule of 9's for Total Body Surface Area (BSA)



Intubate early if you suspect inhalation injury, as airway can become obstructed due to edema.

- immerse in 40-42°C agitated water for 10-30 minutes (very painful; administer adequate analgesia)
- clean injured area, leave injured region open to air
- consider aspiration/debridement of blisters (controversial)
- debride skin gently
- tetanus prophylaxis
- consider penicillin G as frost bite injury at high risk of infection
- surgical intervention may be required to release restrictive eschars
- never allow a thawed area to re-chill/freeze

Burns

- see Plastic Surgery, PL15

Physical Examination

- burn size
 - rule of nines (see Figure 15); does not include 1st degree burns
- burn depth
 - superficial: epidermis only (e.g. sunburn)
 - partial thickness: into superficial dermis deep or hair follicles, sweat glands
 - full thickness: all layers of the skin
 - deep: to fat, muscle, even bone

Management

- remove noxious agent/stop burning process
- establish airway if needed (indicated with burns >40% BSA or smoke inhalation injury)
- resuscitation for 2nd and 3rd degree burns (after initiation of 2 large bore IVs)
 - Parkland Formula: Ringer's lactate 4 cc/kg/%BSA burned; give half in first 8 hours, half in next 16 hours; maintenance fluids are also required if patient cannot tolerate PO hydration
 - urine output is best measure of resuscitation, should be 40-50 cc/hr or 0.5 cc/kg/hr; avoid diuretics
- pain relief – continuous morphine infusion with breakthrough bolus
- investigations: CBC, electrolytes, urinalysis, CXR, ECG, ABG, carboxyhemoglobin
- burn wound care – prevent infection, clean/debride with mild soap and water, sterile dressings
- escharotomy or fasciotomy for circumferential burns (chest, extremities)
- topical antibiotics, systemic antibiotics infrequently indicated
- tetanus prophylaxis if burn is deeper than superficial dermis

Disposition

- admit
 - 2nd degree burns to >10% BSA; any significant 3rd degree burns
 - 2nd degree on face, hands, feet, perineum or across major joints
 - electrical, chemical burns and inhalation injury
 - burn victims with underlying medical problems or immunosuppressed patients

Inhalation Injury

Etiology

- carbon monoxide (CO) poisoning
- direct thermal injury – limited to upper airway
- smoke causes bronchospasm and edema from particulate matter and toxic inhalants (tissue asphyxiates, pulmonary irritants, systemic toxins)

History and Physical

- risk factors: closed space fires, period of unconsciousness, noxious chemicals involved
- cherry red skin (unreliable, usually post-mortem finding)
- singed nasal hairs, soot on oral/nasal membranes, sooty sputum
- hoarseness, stridor, dyspnea
- decreased LOC, confusion
- PO₂ normal but O₂ sat low suggests CO poisoning

Investigations

- measure carboxyhemoglobin levels
- ABG
- CXR ± bronchoscopy

Management

- CO poisoning: 100% O₂ ± hyperbaric O₂ (controversial)
- direct thermal injury: humidified oxygen, early intubation, pulmonary toilet, bronchodilators

Bites

Mammalian Bites

- see [Plastic Surgery](#), PL6
- **history**
 - time and circumstances of bite, symptoms, allergies, tetanus immunization status, comorbid conditions, rabies risks, HIV/hepatitis risk (human bite)
 - high morbidity associated with clenched fist injuries (CFI), “fight bites”
- **physical examination**
 - assess type of wound: abrasion, laceration, puncture, crush injury
 - assess for direct tissue damage: skin, bone, tendon, neurovascular status
- **investigations**
 - if bony injury or infection suspected check for fracture and gas in tissue with x-rays
 - get skull films in children with scalp bite wounds, ± CT to rule out cranial perforation
- **initial management**
 - wound cleansing and copious irrigation as soon as possible
 - irrigate/debride puncture wounds if feasible, but not if sealed or very small openings; avoid hydrodissection along tissue planes
 - debridement is important in crush injuries to reduce infection and optimize cosmetic and functional repair
 - culture wound if signs of infection (erythema, necrosis or pus); obtain anaerobic cultures if wound foul smelling, necrotizing, or abscess; notify lab that sample is from bite wound
- **prophylactic antibiotics**
 - types of infections resulting from bites: cellulitis, lymphangitis, abscesses, tenosynovitis, osteomyelitis, septic arthritis, sepsis, endocarditis, meningitis
 - a 3-5 day course of antibiotics is recommended for all bite wounds to the hand and should be considered in other bites if any high-risk factors present (efficacy not proven)
 - dog and cat bites (pathogens: *Pasteurella multocida*, *S. aureus*, *S. viridans*)
 - ♦ 80% of cat bites, 5% of dog bites become infected
 - ♦ 1st line: amoxicillin + clavulanic acid
 - human bites (pathogens: *Eikenella corrodens*, *S. aureus*, *S. viridans*, oral anaerobes)
 - ♦ 1st line: amoxicillin + clavulanic acid
 - rabies (see [Infectious Diseases](#), ID8)
 - ♦ reservoirs: warm-blooded animals except rodents, lagomorphs (e.g. rabbits)
 - ♦ post-exposure vaccine is effective; treatment depends on local prevalence
 - suturing
 - ♦ vascular structures (i.e. face and scalp) are less likely to become infected, therefore consider suturing
 - ♦ allow avascular structures (i.e. pretibial regions, hands and feet) to heal by secondary intention
 - tetanus immunization if >10 yrs or incomplete primary series



High Risk Criteria for Infection

Wound Factors

- Puncture wounds
- Crush injuries
- Wounds >12 hrs old
- Hand or foot wounds
- Wounds near joints

Patient Factors

- Immunocompromised
- Age >50 years
- Prosthetic joints or valves



Consider Admission if:

- Moderate to severe infections
- Infections in immunocompromised patients
- Not responding to oral Rx
- Penetrating injuries to tendons, joints, CNS
- Open fractures

Snake Bites

- history, physical exam, investigations and initial management similar to mammalian bites
- additional management issues
 - snake bites are rarely fatal but proper precautions must be taken
 - supportive management, observe for compartment syndrome, analgesia, tetanus prophylaxis
 - contact regional Poison Control Centre for consultation
 - constriction band should be placed proximal to bite
 - observe for signs and symptoms of envenomation 15min-2hrs after bite (pain, sweating, edema, chills, weakness, numbness, tingling, HR changes, faintness, ecchymosis, N/V); if no envenomation then remove band and monitor closely for 24 hrs
 - if envenomation present, administer antivenom

Insect Bites

- **Bee Stings**
 - 5 types of reactions to stings (local, large local, systemic, toxic, unusual)
 - history and physical exam key to diagnosis; no lab test will confirm
 - investigations: CBC, electrolytes, BUN, creatinine, glucose, ABGs, ECG
 - ABC management, epinephrine 0.1 mg IV over 5 minutes if shock, antihistamines, cimetidine 300mg IV/IM/PO, steroids, β-agonists for SOB/wheezing 3 mg in 5 mL NS via nebulizer, local site management
- **West Nile Virus** (see [Infectious Diseases](#), ID28)
 - severity: asymptomatic 80%, flu-like symptoms 20%, encephalitis <1%
 - clues: aseptic meningitis/encephalitis in late summer in prevalent area
 - incubation 3-14 days, symptoms last 3-6 days
 - general symptoms: fever, malaise, anorexia, headache, altered mental status, motor weakness, ataxia, extrapyramidal signs, GI signs, myalgias, lymphadenopathy, rash, myocarditis, optic neuritis
 - investigations: CBC, electrolytes, CSF, CT/MRI
 - diagnosis: CSF and serum for serology
 - management: ABCs, IV fluids for dehydration, antibiotics if meningitis (based on CSF analysis), analgesia, antipyretics, interferon-α 2b, ribavirin

Near Drowning

- most common in children <4 yrs and teenagers
- causes lung damage, hypoxemia and may lead to hypoxic encephalopathy
- must also assess for shock, C-spine injuries, hypothermia, scuba-related injuries (barotrauma, air emboli, lung re-expansion injury)
- complications: volume shifts, electrolyte abnormalities, hemolysis, rhabdomyolysis, ATN, DIC

Physical Examination

- ABCs, vitals: watch closely for hypotension
- lungs: rales (ARDS, pulmonary edema), decreased breath sounds (pneumothorax)
- CVS: murmurs, arrhythmias, JVP (CHF, pneumothorax)
- H&N: assess for C-spine injuries
- neuro: GCS or AVPU, pupils, focal deficits

Investigations

- labs: CBC, electrolytes, ABGs, Cr, BUN, urinalysis
- imaging: CXR (pulmonary edema, pneumothorax)
- ECG

Management

- ABCs, treat for trauma, shock, hypothermia
- cardiac and O₂ sat monitors, IV access
- intensive respiratory care
 - ventilator assistance if decreased respirations, pCO₂ >50 mmHg, or pO₂ <60 mmHg on max O₂
 - may require intubation for airway protection, ventilation, pulmonary toilet
 - high flow O₂/CPAP/BiPAP may be adequate but some may need mechanical ventilation with PEEP
- arrhythmias: usually respond to corrections of hypoxemia, hypothermia, acidosis
- vomiting: very common, NG suction to avoid aspiration
- convulsions: usually respond to O₂; if not, diazepam 5-10 mg IV slowly
- bronchospasm: bronchodilators
- bacterial pneumonia: not necessary to prophylax with antibiotics unless contaminated water or hot-tub (*Pseudomonas*)
- must observe for at least 24 hours as non-cardiogenic pulmonary edema may develop late

Disposition

- non-significant submersion – discharge after short observation
- significant submersion (even if asymptomatic) – long period of observation (24 hrs) as pulmonary edema may appear late
- CNS symptoms or hypoxemia – admit
- severe hypoxemia, decreased LOC – ICU

Toxicology



Alcohol Related Emergencies

- see Psychiatry, PS20

Acute Intoxication

- slurred speech, CNS depression, disinhibition, lack of coordination
- nystagmus, diplopia, dysarthria, ataxia → may progress to coma
- frank hypotension (peripheral vasodilation)
- if obtunded rule out
 - head trauma/intracranial hemorrhage
 - associated depressant/street drugs, toxic alcohols
 - ♦ may also contribute to respiratory/cardiac depression
 - hypoglycemia (screen with bedside glucometer)
 - hepatic encephalopathy: confusion, altered LOC, coma
 - ♦ precipitating factors: GI bleed, infection, sedation, electrolyte abnormalities, protein meal
 - Wernicke's encephalopathy (ataxia, ophthalmoplegia, delirium)
 - post-ictal state, basilar stroke



Alcohol levels correlate poorly with intoxication.



Alcohol intoxication may invalidate informed consent.

Withdrawal

- beware withdrawal signs (see Table 22)
- treatment
 - diazepam 10-20 mg IV or PO OR lorazepam 2-4 mg IV or PO q1hr until calm
 - may use CIWA protocol and give benzodiazepines as above until CIWA <10
 - thiamine 100 mg IM then 50-100 mg/day
 - magnesium sulfate 4 g IV over 1-2 h (if hypomagnesemic)
 - admit patients with delirium tremens (DT), arrhythmias, or multiple seizures

Table 22. Alcohol Withdrawal Signs

Time Since Last Drink	Syndrome	Description
6-8 hr	Mild withdrawal	Generalized tremor, anxiety, agitation, but no delirium Autonomic hyperactivity (sinus tachycardia), insomnia, nausea, vomiting
1-2 days	Alcoholic hallucinations	Visual (most common), auditory and tactile hallucinations Vitals often normal
8 hr-2 days	Withdrawal seizures	Typically brief generalized tonic-clonic seizures May have several within a few hours
3-5 days	Delirium tremens (DT)	5% of untreated withdrawal patients Severely confused state, fluctuating levels of consciousness Agitation, insomnia, hallucinations/delusions, tremor Tachycardia, hyperpyrexia, diaphoresis High mortality rate

**CIWA Withdrawal Symptoms**

Nausea and vomiting
Tremor
Paroxysmal sweats
Anxiety
Agitation
Visual disturbances
Tactile disturbances
Auditory disturbances
Headache
Disorientation

10 symptoms each scored out of 7
except orientation is out of 4.

Seizures

- associated with ingestion and withdrawal
- withdrawal seizures
 - occur 8-48 hrs after last drink (typically brief generalized tonic-clonic seizures)
 - if >48 hrs, think of DT (see Table 22)
- prophylaxis: diazepam 20 mg PO q1h x 3 minimum, regardless of CIWA score
- CT head if focal seizures have occurred

Cardiovascular Complications

- HTN
- cardiomyopathy: SOB, edema
- arrhythmias ("holiday heart")
 - atrial fibrillation (most common), atrial flutter, SVT, VT (especially Torsades if hypomagnesemic/hypokalemic)

Metabolic Abnormalities

- alcoholic ketoacidosis
 - history of chronic alcohol intake with abrupt decrease/cessation
 - malnourished, abdominal pain with nausea and vomiting
 - anion gap (AG) metabolic acidosis, urine ketones, low glucose and normal osmolality
 - treatment: dextrose, thiamine (50-100 mg prior to dextrose), volume repletion (with NS)
 - generally resolves in 12-24 hr
- other alcohols
 - ethylene glycol → CNS, CVS, renal findings
 - methanol
 - ◆ early: lethargy, confusion
 - ◆ late: headache, visual changes, N/V, abdominal pain, tachypnea
 - both produce severe metabolic acidosis with AG and osmolar gap
 - EtOH co-ingestion is protective
 - treatment
 - ◆ fomepizole 15 mg/kg IV bolus OR EtOH 10% IV bolus and drip to achieve blood level of 20 mmol/L
 - EtOH loading may be done PO
 - ◆ consider folic acid for methanol and pyridoxime for ethylene glycol – both help reduce conversion to active metabolites
 - ◆ urgent hemodialysis required
- other abnormalities associated with alcohol: hypomagnesemia, hypophosphatemia, hypocalcemia, hypoglycemia, hypokalemia

**Common Deficiencies**

- Thiamine
- Niacin
- Folate
- Glycogen
- Magnesium
- Potassium

Gastrointestinal Abnormalities

- gastritis
 - common cause of abdominal pain and GI bleed in chronic alcohol users
- pancreatitis
 - serum amylase very unreliable in patients with chronic pancreatitis, may need serum lipase
 - hemorrhagic form (15%) associated with increased mortality
 - fluid resuscitation very important
- hepatitis
 - AST/ALT ratio >2 suggests alcohol as the cause as well as elevated GGT with acute ingestion

- peritonitis/spontaneous bacterial peritonitis
 - occasionally accompanies cirrhosis
 - leukocytosis, fever, generalized abdominal pain/tenderness
 - paracentesis for diagnosis (common pathogens: *E. coli*, *Klebsiella*, *Strep*)
- GI bleeds
 - most commonly gastritis or ulcers, even if patient known to have varices
 - consider Mallory-Weiss tear secondary to retching
 - often complicated by underlying coagulopathies
 - minor – treat with antacids
 - severe or recurrent – endoscopy

Miscellaneous Problems

- rhabdomyolysis
 - presents as acute weakness associated with muscle tenderness
 - usually occurs after prolonged immobilization
 - increased creatinine kinase (CK), hyperkalemia
 - myoglobinuria – may lead to acute renal failure
 - treatment: IV fluids, forced diuresis (mannitol 20% 15 mg/kg IV over 30 min)
- increased infections – due to impaired host defenses, immunocompromise, poor living conditions

Disposition

- before patient leaves ED ensure
 - stable vital signs
 - can walk unassisted
 - fully oriented
- offer social services to find shelter or detox program
- ensure patient can obtain any medications prescribed and can complete any necessary follow-up



Approach to the Overdose Patient

History

- who? age, weight, underlying medical problems, medications
- what? substance and how much
- when? time since exposure determines prognosis and need for decontamination, symptoms since
- how? route
- why? intention, suicidality

Physical Examination

- focus on: ABCs, LOC/GCS, vitals, pupils

Principles of Toxicology

- 4 principles to consider with all ingestions
 - I. resuscitation (ABCs)
 - II. screening (toxidrome? clinical clues?)
 - III. decrease absorption of drug
 - IV. increase elimination of drug

ABCs of Toxicology

- basic axiom of care is symptomatic and supportive treatment
- address underlying problem only once patient is stable
 - A Airway (consider stabilizing the C-spine)
 - B Breathing
 - C Circulation
 - D1 Drugs
 - ACLS as necessary to resuscitate the patient
 - universal antidotes
 - D2 Draw bloods
 - D3 Decontamination (decrease absorption)
 - E Expose (look for specific toxidromes)/Examine the Patient
 - F Full vitals, ECG monitor, Foley, x-rays, etc.
 - G Give specific antidotes, treatments
- Go back and reassess
- Call poison information centre
- Obtain corroborative history from family, bystanders



Suspect Overdose when:

- Altered level of consciousness/coma
- Young patient with life-threatening arrhythmia
- Trauma patient
- Bizarre or puzzling clinical presentation

D1 – Universal Antidotes

- treatments that will not harm patients and may be essential

Oxygen

- do not deprive a hypoxic patient of oxygen no matter what the antecedent medical history (i.e. even COPD with CO₂ retention)
- if depression of hypoxic drive, intubate and ventilate
- exception: paraquat or diquat (herbicides) inhalation or ingestion (oxygen radicals increase morbidity)

Glucose

- give to any patient presenting with altered LOC
- measure blood glucose prior to glucose administration if possible
- adults: 0.5-1.0 g/kg (1-2 mL/kg) IV of D50W
- children: 0.25 g/kg (2-4 mL/kg) IV of D25W

Thiamine (Vitamin B1)

- 100 mg IV/IM to all patients with IV/PO glucose
- a necessary cofactor for glucose metabolism, but do not delay glucose if thiamine unavailable
- to prevent Wernicke-Korsakoff syndrome
- must assume all undifferentiated comatose patients are at risk

Naloxone (central μ -receptor competitive antagonist, shorter $t_{1/2}$ than naltrexone)

- antidote for opioids: administration is both diagnostic and therapeutic (1 min onset of action)
- used for the undifferentiated comatose patient
- loading dose
 - adults
 - ♦ 2 mg initial bolus IV/IM/SL/SC or via ETT (ETT dose = 2-2.5x IV dose)
 - ♦ if no response after 2-3 minutes, increase dose by 2 mg increments until a response or to max 10 mg
 - ♦ known chronic user, suspicious history, or evidence of track marks, give 0.01 mg/kg
 - child
 - ♦ 0.01 mg/kg initial bolus IV/IO/ETT
 - ♦ 0.1 mg/kg if no response and narcotic still suspected to max of 10 mg
- maintenance dose
 - may be required because half-life of naloxone (30-80 mins) is much shorter than many narcotics
 - ♦ hourly infusion rate at 2/3 of initial dose that produced patient arousal



Populations at Risk for Thiamine Deficiency

- Alcoholics
- Anorexics
- Hyperemesis of pregnancy
- Malnutrition states



Administration of naloxone can cause opiate withdrawal in chronic users. Minor withdrawal may present as lacrimation, rhinorrhea, diaphoresis, yawning, piloerection, HTN, and tachycardia. Severe withdrawal may present as hot and cold flashes, arthralgias, myalgias, N/V, and abdominal cramps.

D2 – Draw Bloods

- essential tests (see Table 24)
 - CBC, electrolytes, BUN/creatinine, glucose, INR/PTT, osmolality
 - ABGs, measure O₂ sat
 - acetylsalicylic acid (ASA), acetaminophen, EtOH levels
- potentially useful tests
 - drug levels – this is NOT a serum drug screen
 - Ca, Mg, PO₄
 - protein, albumin, lactate, ketones, liver enzymes, CK – depending on drug and clinical presentation

Serum Drug Levels

- treat the patient, not the drug level
- negative tox screen does not rule out a toxic ingestion – signifies only that the specific drugs tested were not detectable in the specimen
- specific drugs available on general screen vary by institution; check before ordering
- urine screens also available (qualitative only)



Plasma Osmolar Gap (POG)
 $= (2 \text{ Na} + \text{glucose} + \text{urea}) - \text{plasma osmolarity}$
 Normal POG < 10 mOsm/kg



Anion Gap (AG)
 $= \text{Na} - \text{Cl} - \text{bicarb}$
 Normal AG ≤ 12 mEq/L

Table 23. Toxic Gaps (see also [Nephrology](#))

METABOLIC ACIDOSIS

Increased AG: "MUDPILES CAT" (* = toxic)

Methanol*
Uremia
Diabetic ketoacidosis/Starvation ketoacidosis
Phenformin*/Paraldehyde*
Isoniazid, Iron, Ibuprofen
Lactate (anything that causes seizures or shock)
Ethylene glycol*
Salicylates*
Cyanide, carbon monoxide*
Alcoholic Ketoacidosis
Toluene, theophylline*

Decreased AG

Electrolyte imbalance (increased Na/K/Mg)
 Hypoalbuminemia (50% fall in albumin ~ 5.5 mmol/L decrease in the AG)
 Li, Br elevation
 Paraproteins (multiple myeloma)

Normal AG

High K: pyelonephritis, obstructive nephropathy, renal tubular acidosis (RTA), IV, TPN
 Low K: small bowel losses, acetazolamide, RTA I, II

Increased POG: "MAE DIE" (if it ends in "-ol", it will likely \uparrow the POG)

Methanol
Acetone
Ethanol
Diuretics (glycerol, mannitol, sorbitol)
Isopropanol
Ethylene glycol

Note: normal osmolar gap does not rule out toxic alcohol; only an elevated gap is helpful

Increased O₂ saturation gap

Carboxyhemoglobin
 Methemoglobin
 Sulfmethemoglobin

Table 24. Use of the Clinical Laboratory in the Initial Diagnosis of Poisoning

Test	Finding	Selected Causes
ABG	Hypoventilation (\uparrow pCO ₂) Hyperventilation (\downarrow pCO ₂)	CNS depressants (opioids, sedative-hypnotic agents, phenothiazines, EtOH) Salicylates, CO, other asphyxiants
Electrolytes	\uparrow anion-gap metabolic acidosis Hyperkalemia Hypokalemia	"MUDPILES CAT" : see "Metabolic Acidosis" above Digitalis glycosides, fluoride, potassium Theophylline, caffeine, beta-adrenergic agents, soluble barium salts, diuretics, insulin
Glucose	Hypoglycemia	Oral hypoglycemia agents, insulin, EtOH, ASA
Osmolality and Osmolar Gap	Elevated osmolar gap	"MAE DIE" : see "Toxic Gaps" above
ECG	Wide QRS complex Prolonged QT interval Atrioventricular block	TCAs, quinidine, other class Ia and Ic antiarrhythmic agents Quinidine and related antiarrhythmics, terfenadine, astemizole, antipsychotics Ca antagonists, digitalis glycosides, phenylpropanolamine
Abdominal X-Ray	Radiopaque pills or objects	"CHIPES" : Calcium, Chloral hydrate, CCl ₄ , Heavy metals, Iron, Potassium, Enteric coated Salicylates, and some foreign bodies
Serum Acetaminophen	Elevated level (> 140 mg/L or 1000 μ mol/L 4 hours after ingestion)	May be only sign of acetaminophen poisoning

D3 – Decontamination and Enhanced Elimination

Ocular Decontamination

- saline irrigation to neutralize pH; alkali exposure requires ophthalmology consult

Dermal Decontamination (wear protective gear)

- remove clothing, brush off toxic agents, irrigate all external surfaces

Gastrointestinal Decontamination

- single dose activated charcoal (SDAC) (see Table 27 for drug toxidromes that are treated with charcoal)
 - adsorption of drug/toxin to AC prevents availability
 - contraindications: caustics, SBO, perforation
 - dose: 10g/g drug ingested or 1g/kg body weight
 - odourless, tasteless, prepared as slurry with H₂O
- whole bowel irrigation
 - 500 mL (child) to 2000 mL (adult) of polyethylene glycol solution/hour by mouth until clear effluent per rectum
 - start slow (500 mL in an adult) and aim to increase rate hourly as tolerated
 - indications
 - ♦ awake, alert, can be nursed upright
 - ♦ delayed release product
 - ♦ drug/toxin not bound to charcoal
 - ♦ drug packages (if any evidence of breakage \rightarrow emergency surgery)
 - ♦ recent toxin ingestion



Substances NOT Adsorbed by Activated Charcoal

- Lithium
- Iron
- Alcohols
- Lead
- Caustics

- contraindications
 - evidence of ileus, perforation, or obstruction
- surgical removal in extreme cases
 - indicated for drugs that are toxic, form concretions, or cannot be removed by conventional means
- no evidence for the use of cathartics (or ipecac)

EXTRA-CORPOREAL DRUG REMOVAL (ECDR)

Urine Alkalinization

- may be used for: ASA, methotrexate, phenobarbital, chlorpropamide
- weakly acidic substances can be trapped in alkali urine (pH >7.5) to increase elimination

Multidose Activated Charcoal (MDAC)

- may be used for: carbamazepine, phenobarbital, quinine, theophylline
- for toxins which undergo enterohepatic recirculation
- removes drug that has already been absorbed by drawing it back into GI tract
- various regimens: 12.5 g (1/4 bottle) PO q1h or 25 g (1/2 bottle) PO q2h until non-toxic

Hemodialysis

- indications/criteria for hemodialysis
 - toxins that have high water solubility, low protein binding, low molecular weight, adequate concentration gradient, small volume of distribution (Vd) or rapid plasma equilibration
 - removal of toxin will cause clinical improvement
 - advantage is shown over other modes of therapy
 - predicted that drug or metabolite will have toxic effects
 - impairment of normal routes of elimination (cardiac, renal, or hepatic)
 - clinical deterioration despite maximal medical support
- useful for the following blood toxins:
 - methanol
 - ethylene glycol
 - salicylates
 - lithium
 - phenobarbital: 430-650 mmol/L
 - chloral hydrate (→ trichloroethanol): >200 mg/kg
- others include theophylline, carbamazepine, valproate, methotrexate

E – Examine the Patient

- vital signs (including temperature), skin (needle tracks, colour), mucous membranes, pupils, odours and CNS
- head-to-toe survey including
 - C-spine
 - signs of trauma, seizures (incontinence, “tongue biting”, etc.), infection (meningismus), chronic alcohol/drug abuse (track marks, nasal septum erosion)
- mental status

Table 25. Specific Toxicodromes

Toxidrome	Overdose Signs and Symptoms	Examples of Drugs
Anticholinergics	Hyperthermia	Antidepressants (e.g. TCAs)
	Dilated pupils	Cyclobenzaprine (Flexeril®)
	Dry skin	Carbamazepine
	Vasodilation	Antihistamines (e.g. diphenhydramine)
	Agitation/hallucinations	Antiparkinsonians
	Ileus	Antipsychotics
	Urinary retention	Antispasmodics
	Tachycardia	Belladonna alkaloids (e.g. atropine)
Cholinergics	“DUMBELS”	Natural plants: mushrooms, trumpet flower
	Diaphoresis, D iarrrhea, D ecreased blood pressure	Anticholinesterases: physostigmine,
	Urination	Insecticides (organophosphates, carbamates)
	Miosis	Nerve gases
	Bronchospasm, B ronchorrhea, B radycardia	
	Emesis, Excitation of skeletal muscle	
	Lacrimation	
	Salivation, S eizures	
Extrapyramidal	Dysphonia, dysphagia	Major tranquilizers
	Rigidity and tremor	Antipsychotics
	Motor restlessness, crawling sensation (akathisia)	
	Constant movements (dyskinesia)	
	Dystonia (muscle spasms, laryngospasm, trismus, oculogyric crisis, torticollis)	



Table 25. Specific Toxidromes (continued)

Toxidrome	Overdose Signs and Symptoms	Examples of Drugs
Hemoglobin Derangements	Increased respiratory rate Decreased level of consciousness Seizures Cyanosis unresponsive to O ₂ Lactic acidosis	Carbon monoxide poisoning (carboxyhemoglobin) Drug ingestion (methemoglobin, sulfmethemoglobin)
Narcotics, Sedatives/Hypnotics, EtOH	Hypothermia Hypotension Respiratory depression Dilated or constricted pupils (pinpoint in opiate OD) CNS depression	EtOH Benzodiazepines Opiates (morphine, heroin, etc.) Barbiturates GHB
Sympathomimetics	Increased temperature CNS excitation (including seizures) Tachycardia, hypertension Nausea and vomiting Diaphoresis Dilated pupils	Amphetamines, caffeine, cocaine, LSD, PCP Ephedrine and other decongestants Thyroid hormone Sedatives, EtOH withdrawal
Serotonin Syndrome	Mental status changes, autonomic hyperactivity, neuromuscular abnormalities, hyperthermia, diarrhea, HTN	MAOI, TCA, SSRI, opiate analgesics Cough medicine, weight reduction medications

Note: ASA poisoning and hypoglycemia mimic sympathomimetic toxidrome

G – Give Specific Antidotes and Treatments



Urine Alkalinization Treatment for ASA Overdose

- urine pH >7.5
- fluid resuscitate first, then 3 amps NaHCO₃/litre of D5W @ 1.5 x maintenance
- add 20-40 mEq KCl/litre if patient is able to urinate

Table 26. Protocol for Warfarin Overdose

INR	Management
<5.0	Cessation of warfarin administration, observation, serial INR/PT
5.1–9.0	If no risk factors for bleeding, hold warfarin x 1-2 days and reduce maintenance dose OR Vitamin K 1-2 mg PO if patient at increased risk of bleeding or fresh frozen plasma (FFP) if active bleed
9.1–20.0	Hold warfarin, Vitamin K 2-4 mg PO, serial INR/PT, additional Vitamin K if necessary or FFP if active bleed
>20.0	FFP 10-15 mL/kg, Vitamin K 10 mg IV over 10 min, increase Vitamin K dosing (q4h) if needed

Table 27. Specific Antidotes and Treatments – call local poison information centre for specific doses and treatment recommendations

Toxin	Treatment	Considerations
Acetaminophen	Decontaminate (activated charcoal) N-acetylcysteine	Often clinically silent; evidence of liver/renal damage delayed >24 hrs Toxic dose >200 mg/kg (>7.5 g adult) Monitor drug level immediately and 4 hrs post-ingestion; also liver enzymes, INR, PTT, BUN, Cr Hypoglycemia, metabolic acidosis, encephalopathy → poor prognosis
ASA	Decontaminate (activated charcoal) Alkalinize urine; want urine pH >7.5	Monitor serum pH and drug levels closely Monitor K level; may require supplement for urine alkalinization Hemodialysis may be needed if intractable metabolic acidosis, very high levels, or end-organ damage (i.e. unable to diurese)
Anticholinergics	Decontaminate (activated charcoal) Supportive care	Special antidotes available. Consult Poison Information Centre (PIC)
Benzodiazepines	Decontaminate (activated charcoal) Supportive care	
β-blockers	Decontaminate (activated charcoal) Consider glucagon or high dose insulin euglycemia therapy (HDIE)	Consult PIC
Calcium Channel Blockers	CaCl ₂ 1-4 g of 10% sol'n IV if hypotensive Atropine or isoproterenol if severe Other: HDIE inotropes or aggressive supportive therapy	Order ECG, electrolytes (especially Ca, Mg, Na, K), glucagon may help (2-5 mg)
Cyanide	Cyanide antidote kit or hydroxycobalamin	

Table 27. Specific Antidotes and Treatments – call local poison information centre for specific doses and treatment recommendations (continued)

Toxin	Treatment	Considerations
Digoxin	Decontaminate (activated charcoal) Digoxin-specific Ab fragments 10-20 vials IV if acute; 3-6 if chronic 1 vial (40 mg) neutralizes 0.5 mg of toxin	Use for life-threatening arrhythmias unresponsive to conventional therapy, 6 hr serum digoxin >19 nmol/L, initial K >5 mM, ingestion >10 mg (adult) / >4 mg (child) Common arrhythmias include VFib, VTach, and conduction blocks
Acute Dystonic Rxn	Benztropine: 1-2 mg IM/IV then 2 mg PO x 3 days OR Diphenhydramine 1-2 mg/kg IV, then 25 mg PO qid x 3 days	Benzotropine (Cogentin®) has euphoric effect and potential for abuse
Heparin	Protamine sulfate 25-50 mg IV	For unfractionated heparin overdose only
Insulin/ Oral Hypoglycemic	Glucose IV/PO/NG tube Glucagon: 1-2 mg IM (if no access to glucose)	Glyburide carries highest risk of hypoglycemia among oral agents Consider octreotide for oral hypoglycemics (50-100 µg SC q6h) in these cases; consult local PIC
Ethanol	Thiamine 100 mg IM/IV Manage airway and circulatory support	Hypoglycemia very common in children Mouthwash = 70% EtOH; perfumes and colognes = 40-60% EtOH Order serum EtOH level and glucose level; treat glucose level appropriately
Ethylene Glycol/ Methanol	Ethanol (10%) 10 ml/kg over 30 min, then 1.5 ml/h or fomepizole (4-methylpyrazole) 15 mg/kg IV load over 30 min, then 10 mg/kg q12h	CBC, electrolytes, glucose, ethanol level Consider hemodialysis
CO Poisoning	See ER46	
Opioids	See ER51	
TCAs	Aggressive supportive care NaHCO ₃ bolus for wide QRS/seizures	Flumazenil antidote contraindicated in combined TCA and benzodiazepine overdose Also consider cardiac and hypotension support, gastric decontamination, seizure control Intralipid therapy (consult local PIC)
MDMA	Decontaminate (activated charcoal), supportive care	Monitor CK; treat rhabdomyolysis with high flow fluids
Cocaine	Decontaminate (activated charcoal) if oral Aggressive supportive care	β-blockers are contraindicated in acute cocaine toxicity

Disposition from the Emergency Department

- methanol, ethylene glycol
 - delayed onset, admit and watch clinical and biochemical markers
- TCAs
 - prolonged/delayed cardiotoxicity warrants admission to monitored (ICU) bed
 - if asymptomatic and no clinical signs of intoxication: 6 hour ED observation adequate with proper decontamination and no ECG abnormalities
 - sinus tachycardia alone (most common finding) with history of OD warrants observation in ED
- hydrocarbons/smoke inhalation
 - pneumonitis may lag 6-8 hours
 - consider observation for repeated clinical and radiographic examination
- ASA, acetaminophen
 - if borderline level, get second level 2-4 hours after first
 - for ASA must have at least 2 levels going down before discharge (3 levels minimum)
- oral hypoglycemics
 - admit all patients for minimum 24 hours if hypoglycemic
 - observe asymptomatic patient for at least 8 hours

Psychiatric Consultation

- once patient medically cleared, arrange psychiatric intervention if required
- beware – suicidal ideation may not be expressed

Psychiatric Emergencies

Approach to Common Psychiatric Presentations

- see [Psychiatry](#)
- before seeing patient, ensure your own safety; have security/police available if necessary

History

- safety
 - assess suicidality: suicidal ideation, intent, plan, lethal means, past attempts
 - assess homicidality: access to weapons, intended victim, history of violence
 - command hallucinations
- identify current stressors and coping strategies
- mood symptoms: manic, depressive
- anxiety: panic attacks, generalized anxiety, phobias, OCD, PTSD
- psychotic symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behaviour, negative symptoms (affective flattening, alogia, avolition)
- substance use history: most recent use, amount, previous withdrawal reactions
- past psychiatric history, medications, adherence with medications
- medical history: obtain collateral if available

Physical

- complete physical exam focusing on: vitals, neurological exam, signs of head trauma, signs of drug toxicity, signs of metabolic disorder
- mental status exam: general appearance, behavior, cooperation, speech, mood and affect, thought content and form, perceptual disturbances, cognition (including MMSE if indicated), judgment, insight, reliability

Investigations

- investigations vary with: age, established psychiatric diagnosis vs. first presentation, history and physical suggestive of organic cause
- as indicated: blood glucose, urine and serum toxicology screen, pregnancy test, electrolytes, TSH, AST/ALT, bilirubin, serum creatinine, BUN, osmolality
- blood levels of psychiatric medications
- CT head if suspect neurological etiology
- LP if indicated



Acute Psychosis

Differential Diagnosis

- primary psychotic disorder (e.g. schizophrenia)
- secondary to medical condition (e.g. delirium)
- drugs: substance intoxication or withdrawal, medications (e.g. steroids, anticholinergics)
- infectious (CNS)
- metabolic (hypoglycemic, hepatic, renal, thyroid)
- structural (hemorrhage, neoplasm)

Management

- violence prevention
 - remain calm, empathic and reassuring
 - ensure safety of staff and patients, have extra staff and/or security on hand
 - patients demonstrating escalating agitation or overt violent behavior may require physical restraint and/or chemical tranquilization (see *Violent Patient*, ER57)
- treat agitation: whenever possible, offer medication to patients as opposed to administering with force (helps calm and engage patient)
 - benzodiazepines – lorazepam 2 mg PO, IM or SL
 - antipsychotics – olanzapine 5 mg PO, haloperidol 5 mg PO/IM
- treat underlying medical condition
- psychiatry or Crisis Intervention Team consult



Key Functions of Emergency Psychiatric Assessment

1. Is the patient medically stable?
2. Rule out medical cause
3. Is psychiatric consult needed?
4. Are there safety issues (SI, HI)?
5. Is patient certifiable? (must demonstrate risk [present/past test] and apparent mental illness [future test])



Features that suggest Organic Etiology

Age > 40 years old
 Babbling (incoherent speech or speech difficulties)
 Concerning vital signs
 Disorientation
 Emotional lability
 Fluctuating course
 Global impairment of cognitive function
 Headaches
 Immodesty
 Just started (sudden onset)
 K
 Loss of consciousness
 Movement abnormalities (tremor, ataxia, psychomotor retardation)
 Neurological findings (focal)
 Other abnormalities on physical exam
 Perceptions (visual hallucinations)

Suicidal Patient

Epidemiology

- attempted suicide F>M, completed suicide M>F
- second leading cause of death in people <24 years

Management

- ensure patient safety: close observation, remove potentially dangerous objects from person and room
- assess thoughts (ideation), means, action (preparatory, practice attempts), previous attempts
- admit if there is evidence of intent and organized plan, access to lethal means, psychiatric disorder, intoxication (suicidal ideation may resolve with few days of abstinence)
- patient may require certification if unwilling to stay voluntarily
- do not start long-term medications in the emergency department
- psychiatry or crisis team consult

Violent Patient

Differential Diagnosis

- rule out lethal organic cause (e.g. EtOH, drugs, and head injuries)

Prevention

- be aware and look for prodromal signs of violence: anxiety, restlessness, defensiveness, verbal attacks
- try to de-escalate the situation: address the patient's anger, empathize

Restraints

- pharmacological
 - often necessary – may mask clinical findings and impair exam
 - haloperidol 5-10 mg IM (be prepared for dystonic reactions, especially with multiple doses of neuroleptics over a short period) + lorazepam 2 mg IM/IV
 - look for signs of anticholinergic overdose first (see Table 25)
 - benzodiazepines best option if suspected substance-induced violence
- physical
 - present option to patient in firm but non-hostile manner
 - sufficient people to carry it out safely
 - restrain supine or on side; preferably 4-point restraints, never less than 2-points (opposite arm and leg)
 - suction and airway support available in case of vomiting
- once restrained, search person/clothing for drugs and weapons



See **Psychiatry**, PS24 for certification considerations



High Risk Patients

SAD PERSONS

Sex = male
Age >45 years old
Depression
Previous attempts
Ethanol use
Rational thinking loss
Suicide in family
Organized plan
No spouse, no support system
Serious illness

Common Pediatric ER Presentations

Modified Coma Score

Table 28. Modified GCS

Modified GCS for Infants

Eye Opening	Verbal Response	Motor Response
4 – spontaneously	5 – coos, babbles	6 – normal, spontaneous movement
3 – to speech	4 – irritable cry	5 – withdraws to touch
2 – to pain	3 – cries to pain	4 – withdraws to pain
1 – no response	2 – moans to pain	3 – decorticate flexion
	1 – no response	2 – decerebrate extension
		1 – no response

Modified GCS for Children <4 years

Eye Opening	Verbal Response	Motor Response
4 – spontaneously	5 – oriented, social, speaks, interacts	6 – normal, spontaneous movement
3 – to speech	4 – confused speech, disoriented, consolable	5 – localizes pain
2 – to pain	3 – inappropriate words, not consolable/aware	4 – withdraws to pain
1 – no response	2 – incomprehensible, agitated, restless, not aware	3 – decorticate flexion
	1 – no response	2 – decerebrate extension
		1 – no response



Any infant <1 year of age with a large, boggy scalp hematoma requires CT.



Respiratory Distress



In pediatric respiratory distress, must also rule out:

- Anaphylaxis
- Foreign body
- Pneumonia
- Bronchiolitis

- see also [Pediatrics](#)

History and Physical Examination

- infants not able to feed, older children not able to speak in full sentences
- anxious, irritable, lethargic – may indicate hypoxia
- tachypnea >60 (>40 if preschool age, >30 if school age), retractions, tracheal tug
 - see [Pediatrics](#) Table 1 for age specific vital signs
- pulsus paradoxus
- wheezing, grunting, vomiting

Table 29. Stridorous Upper Airway Diseases: Diagnosis

Feature	Croup	Bacterial Tracheitis	Epiglottitis ¹
Age Range (yrs)	0.5-4	5-10	2-8
Prodrome	Days	Hrs to days	Minutes to hrs
Temperature	Low grade	High	High
Radiography	Steeple sign	Exudates in trachea	Thumb sign
Etiology	Parainfluenza	<i>S. aureus</i> /GAS	<i>H. flu</i> type b
Barky Cough	Yes	Yes	No
Drooling	Yes	No	Yes
Appear Toxic	No	Yes	Yes
Intubation? ICU?	No	Yes	Yes
Antibiotics	No	Yes	Yes
NOTE:			No oral exam

¹Now rare with Hib vaccine in common use



Admission Criteria for Croup

- Stridor at rest or significant respiratory distress
- Relapse after 2 doses of epinephrine or incomplete response
- Co-morbid respiratory or underlying condition

- **management of croup (laryngotracheitis caused by parainfluenza viruses)**
 - humidified O₂ should not be given (no evidence for efficacy)
 - racemic epinephrine q1h x 3 doses, observe for 'rebound effects'
 - dexamethasone x 1 dose
 - consider bacterial tracheitis/epiglottitis if unresponsive to croup therapy
- **management of bacterial tracheitis**
 - start croup therapy, but may have poor response
 - usually require intubation, ENT consult, ICU
 - start antibiotics (e.g. cloxacillin), pending C&S
- **management of epiglottitis**
 - 4 D's: drooling, dyspnea, dysphagia, dysphonia + tripod sitting
 - do not examine oropharynx or agitate patient
 - immediate anaesthesia, ENT call – intubate
 - then IV fluids, Abx, blood cultures
- **management of asthma**
 - supplemental O₂ if sats <90% or PaO₂ <60%
 - bronchodilator therapy: salbutamol (Ventolin®) 0.15 mg/kg by masks q20 min x 3
 - add 250-500 µg ipratropium (Atrovent®) to first 3 doses salbutamol
 - give corticosteroid therapy as soon as possible after arrival (prednisolone 2 mg/kg, dexamethasone 0.3 mg/kg)
 - MgSO₄ if critically ill, not responding to inhaled bronchodilators, steroids; give IV bolus, then infusion
 - IV β₂-agonists if critically ill and not responding to above



Admission Criteria for Asthma

- Respiratory distress 6 hrs after steroids
- Ventolin required > q3h
- Need for supplemental oxygen
- Consider if previous ICU admission



Rochester Criteria for Febrile Infants Age 28-90 Days Old

- Non-toxic looking
- Previously well (>37 weeks GA, home with mother, no hyperbilirubinemia, no prior antibiotics or hospitalizations, no chronic/underlying illness)
- No skin, soft tissue, bone, joint, or ear infection on physical exam
- WBC 5000-15,000, bands <1500; urine <10 WBC/HPF, stool <5 WBC/HPF

Febrile Infant and Febrile Seizures

FEBRILE INFANT

- see also [Pediatrics](#)
- for fever >38°C without obvious focus
 - <28 days
 - ♦ admit
 - ♦ full septic work up (CBC & diff, blood C&S, urine C&S, CSF, CXR if indicated)
 - ♦ treat empirically with broad spectrum IV antibiotics
 - 28-90 days
 - ♦ as above unless infant meets Rochester criteria (see sidebar)
 - >90 days
 - ♦ toxic: admit, treat, full septic workup
 - ♦ non-toxic and no focus: investigate as indicated by history and physical

FEBRILE SEIZURES

- see [Pediatrics](#), P52

Etiology

- children aged 6 months to 5 years with fever or history of recent fever
- simple vs. complex febrile seizures
- normal neurological exam afterward
- no evidence of intracranial infection or history of previous non-febrile seizures
- often positive family history of febrile seizures
- relatively well looking after seizure

Investigations and Management

- if it is a febrile seizure: treat fever and look for source of fever
- if not a febrile seizure: treat seizure and look for source of seizure
 - note: may also have fever but may not meet criteria for febrile seizure

Table 30. Simple vs. Complex Febrile Seizures

Characteristic	Simple	Complex
Duration	< 15 min	> 15 min
Type of Seizure	Generalized	Focal features
Frequency	1 in 24 hours	> 1 in 24 hours

Abdominal Pain

- see also [Pediatrics](#), P41

History

- nature of pain, associated fever
- associated GI, GU symptoms
- anorexia, decreased fluid intake

Physical Examination

- HEENT, respiratory, abdominal exam including DRE, testicular/genital exam

Table 31. Differential Diagnosis of Abdominal Pain in Infants/Children/Adolescents

Medical	Surgical
Colic	Malrotation with volvulus
UTI	Hirschprung's
Constipation	Necrotizing enterocolitis
Gastroenteritis	Incarcerated hernia
Sepsis	Intussusception
HSP (Henoch Schonlein purpura)	Duodenal atresia
Inflammatory Bowel Disease	Appendicitis
HUS (Hemolytic Uremic Syndrome)	Cholecystitis
Pneumonia	Pancreatitis
Strep Throat	Testicular torsion
SCD crisis	Ectopic pregnancy
DKA	Trauma
Functional	Pyloric stenosis

*Remember to keep an index of suspicion for child abuse

Common Infections

- see also [Pediatrics](#)

Table 32. Antibiotic Treatment of Pediatric Bacterial Infections

Infection	Pathogens	Treatment
MENINGITIS		
SEPSIS		
Neonatal	GBS, <i>E. coli</i> , <i>Listeria</i> , <i>S. aureus</i> , Gram-negative bacilli	<ul style="list-style-type: none"> • ampicillin + aminoglycoside (gentamicin or • ampicillin + cefotaxime ± cloxacillin if risk of <i>S. aureus</i>
1-3 months	Same pathogens as above and below	• ampicillin + cefotaxime ± cloxacillin if risk of <i>S. aureus</i>
>3 months	<i>S. pneumococcus</i> , <i>H. influenzae</i> type b (>5 yrs), meningococcus	<ul style="list-style-type: none"> • cefuroxime • ceftriaxone or cefotaxime, if risk of meningitis • vancomycin, if penicillin/cephalosporin-resistant pneumococci
OTITIS MEDIA		
1st line	<i>S. pneumoniae</i> , <i>H. influenzae</i> type b, <i>M. Catarrhalis</i>	• amoxicillin 80-90 mg/kg per day
2nd line		• amoxicillin-clavulanate (Clavulin®)
Treatment failure		• high dose Clavulin® or cefuroxime or ceftriaxone
STREP PHARYNGITIS		
	Group A beta-hemolytic <i>Streptococcus</i>	• penicillin/amoxicillin or erythromycin (penicillin allergy)
UTI		
	<i>E. coli</i> , <i>Proteus</i> , <i>H. influenzae</i> , <i>Pseudomonas</i> , <i>S. saprophyticus</i> Enterococcus, GBS	<ul style="list-style-type: none"> • amoxicillin/ampicillin or • trimethoprim-sulfamethoxazole
PNEUMONIA		
1-3 months	Viral, <i>S. pneumoniae</i> , <i>C. trachomatis</i> , <i>B. pertussis</i> , <i>S. aureus</i> , <i>H. influenzae</i>	• cefuroxime ± macrolide (erythromycin) or ampicillin ± macrolide
3 months-5 years	Viral, <i>S. pneumoniae</i> , <i>S. aureus</i> , <i>H. influenzae</i> , <i>Mycoplasma pneumoniae</i>	• ampicillin/amoxicillin or cefuroxime
>5 years	As above	• ampicillin/amoxicillin + macrolide or cefuroxime + macrolide

Child Abuse and Neglect

- see also [Pediatrics](#)
- obligation to report **any** suspected/known case of child abuse or neglect to CAS yourself (do not delegate)
- document injuries
- consider skeletal survey x-rays, ophtho consult, CT head
- injury patterns associated with child abuse
 - head injuries: torn frenulum, dental injuries, bilateral black eyes, traumatic hair loss, diffuse severe CNS injury, retinal hemorrhage
 - Shaken Baby Syndrome: diffuse brain injury, subdural/subarachnoid hemorrhage, retinal hemorrhage, minimal/no evidence of external trauma, associated bony fractures
 - skin injuries: bites, bruises/burns in shape of an object, glove/stocking distribution of burns, bruises of various ages, bruises in protected areas
 - bone injuries: rib fractures without major trauma, femur fractures age <1 year of age, spiral fractures of long bones in non-ambulatory children, metaphyseal fractures in infants, multiple fractures of various ages, complex/multiple skull fractures
 - genitourinary/gastrointestinal injuries: chronic abdominal/perineal pain, injury to genitals/rectum, STI/pregnancy, recurrent vomiting or diarrhea



Presentation of Neglect

- Failure to thrive, developmental delay
- Inadequate or dirty clothing, poor hygiene
- Child exhibits poor attachment to parents, no stranger anxiety

Procedural Sedation

- procedural sedation: the technique of sedative or dissociative agent administration with or without analgesics to induce a state that allows a patient to tolerate an unpleasant or painful procedure while maintaining all protective cardiorespiratory functions (i.e. a depressed level of consciousness without loss of a patient's protective airway reflexes)
 - must weigh degree of pain and expected relief versus risk/complications of sedation and procedure
- examples of procedures that may require sedation in the emergency department:
 - setting fractures, reducing dislocations, draining abscesses, exploring wounds/ulcers/superficial infections, endoscopic examination
 - may also be required to reduce patient agitation if imaging is acutely required

Requirements for Safe Procedural Sedation in the Emergency Department

- airway suitable for safe intubation and ventilation
- appropriate equipment/personnel available
- intact and functioning cardiorespiratory and neurological system
- ideally, NPO for minimum 4-6 hours
- anesthetic history and drug allergies, including manifestations
- appropriate IV access, monitoring (oxygen saturation, BP, HR, etc.)
- informed consent obtained

Common Procedural Sedation Medications (titrate to effect)

- see *Common Medications*, below

Common Medications

Table 33. Commonly Used Medications

Drug	Dosing Schedule	Indications	Comments
fentanyl	0.5-1.0 µg/kg IV	Procedural sedation	Very short acting narcotic (complication=apnea)
midazolam	50 µg/kg IV	Procedural sedation	Short acting benzodiazepine (complication=apnea when used with narcotic) Fentanyl and midazolam often used together for procedural sedation
propofol	0.25-0.5 mg/kg IV	Procedural sedation	Short acting Anesthetic/sedative (complication=apnea, decreased BP)
flumazenil	0.3 mg IV bolus q5min x 3doses	Reversal of procedural sedation	Benzodiazepine antagonist NB don't use in chronic benzodiazepine user
lidocaine with epi	max 7 mg/kg SC	Local anesthetic	Not to be used in fingers, nose, toes, penis, ears
lidocaine w/o epi	max 5 mg/kg SC	Local anesthetic	
Polysporin®	apply to affected area bid-tid	Superficial infections	
morphine	15-30 mg PO q8-12h 0.1-0.2 mg/kg max 15 mg IV q4h	Mild to moderate acute/chronic pain Prescribed in combination with NSAIDs or acetaminophen	GI and constipation side effects DO NOT CRUSH, CUT or CHEW
Percocet 10/325®	1-2 tabs PO q6h prn	Moderate pain control	Oxycodone + acetaminophen Max 4 g acetaminophen daily
acetaminophen	325-650 mg PO q4-6h prn	Pain control	Max 4 g daily
Tylenol #3®	1-2 tabs PO q4-6h prn	Pain control	Max 4 g acetaminophen daily
Ibuprofen	200-800 mg PO tid prn max 1200 mg/d	Mild to moderate acute pain Analgesia and anti-inflammatory properties	
thiamine	Wernicke's encephalopathy: 100 mg IV/IM initially then 50-100 mg IM/IV OD/PO x 3d	To treat/prevent Wernicke's encephalopathy	Caution use in pregnancy
diazepam	anxiety: 2-10 mg PO tid/qid alcohol withdrawal: 10-20 mg PO/IV q1h titrated to signs/symptoms	Anxiety Alcohol withdrawal	
lorazepam	anxiety: 0.5-2 mg PO/IM/IV q6-8h status epilepticus: 4 mg IV repeat up to q5min	Anxiety Status epilepticus	
phenytoin	status epilepticus: see Table 13	Status epilepticus	Begin maintenance dose 12hr after loading dose Continuous ECG, BP monitoring mandatory
epinephrine	anaphylaxis: 0.1-0.5 mg IM; can repeat q10-15min	Anaphylaxis	Max 1 mg/dose

Table 33. Commonly Used Medications (continued)

Drug	Dosing Schedule	Indications	Comments
salbutamol	2 puffs inhaled q4-6h (4yrs) max 12 puffs/day	Asthma	Caution with cardiac abnormalities
ipratropium bromide	2-3 puffs inhaled tid-qid, max 12 puffs/day	Asthma	Contraindicated with peanut/soy allergy Caution with narrow-angle glaucoma
nitroglycerin	acute angina: 0.3-0.6 mg SL q5min, OR 5 µg/min IV increasing by 5-20 µg/min q3-5min	Angina Acute MI	Not to be used with other anti-hypertensives
ASA	325-650 mg PO q4h max 4g/day stroke/MI risk: 81-325 mg PO OD	Pain control Cardiac prevention	
β-blockers (metoprolol)	5 mg slow IV q5min x 3 if no contraindications	Acute MI	
enoxaparin	1 mg/kg SC BID	Acute MI	
insulin	bolus 5-10 U (0.2 U/kg) then 5-10 U (0.1 U/kg) per hour	Hyperglycemia	Monitor blood glucose levels Consider K replacement, also measure blood glucose levels before administration
glucose	0.5-1.0 g/kg (1-2 ml/kg) IV of D50W	Hypoglycemia/DKA	
furosemide (Lasix®)	CHF: 40-80 mg IV HTN: 10-40 mg PO BID	CHF HTN	Monitor for electrolyte imbalances
haloperidol	2.5-5.0 mg PO/IM initial effective dose 6-20 mg/day	Psychosis	Monitor with Parkinson's; results in CNS depression
naloxone	0.5-2 mg or 0.01-0.02 mg/kg initial bolus IV/IM/SL/SC or via ETT (2-2.5x IV dose), increase dose by 2 mg until response/max 10 mg	Comatose patient Opioid overdose Reversal in procedural sedation	
activated charcoal	30-100 g PO in 250 ml H ₂ O	Poisoning/overdose	

References

Books

Cecil's Essentials of Medicine 7th ed. Andreoli TE, Carpenter CJ, Griggs RC, Benjamin IJ. Saunders, 2007.
 Clinical Anesthesia 4th ed. Barash PG, Cullen BF, Stoelting RK. Philadelphia: Lippincott, 2001.
 Clinical procedures in emergency medicine. 3rd ed. Roberts JR and Hedges JR (ed). WB Saunders Co, 1998.
 Emergency medicine: A comprehensive study guide, 5th ed. Tintinalli JE and Kelen GE (ed). McGraw-Hill Professional Publishing, 1999.
 Emergency Medicine On Call. Keim, Setal. McGraw Hill. 2004.
 Emergency Medicine Recall. Woods, WA et al (ed). Lippincott Williams and Wilkins, 2000.
 Physiologic and Pharmacologic Bases of Anesthesia. Collins VJ. Pennsylvania: Williams & Wilkins, 1996.
 Practical Guide to the Care of the Medical Patient, 5th ed. Ferri F (ed). Mosby, 2001.
 Principles of Medical Pharmacology. Kalant H, Roschlau WH New York: Oxford University Press, 1998.
 Rosen's Emergency Medicine: Concepts and Clinical Practice, 5th ed. Marx (ed). Mosby 2002.

Journal Articles

American college of emergency physicians: clinical policy for the initial approach to patients presenting with altered mental status. Ann Emerg Med Feb 1999; 33:251-280
 Bachmann LM, Kolb E, Koller MT, Steurer J, ter Riet G. Accuracy of Ottawa ankle rules to exclude fractures of the ankle and mid-foot: systematic review. BMJ 2003; 326(7386):417.
 Chu, P. Blunt Abdominal Trauma: current concepts. Current Orthopedics 2003; 17, 254-259.
 Dargan P, Wallace C, Jones AL. An evidence based flowchart to guide the management of acute salicylate (aspirin) overdose. Emerg Med J. 2002; 19:206-209.
 Elliott WJ. Hypertensive emergencies. Crit Care Clin. 2001; 17(2):435-51.
 Epstein M. Diagnosis and management of hypertensive emergencies. Clin Cornerstone. 1999; 2(1):41-54.
 Frampton A. Reporting of gunshot wounds by doctors in emergency departments: A duty or a right? Some legal and ethical issues surrounding breaking patient confidentiality. Emerg. Med. J. 2005; 22:84-86
 Kline JA, Mitchell AM, Kabrhel C, Richman PB, Courtney DM. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. J Thromb Haemost 2004; 2(8):1247-55.
 Munro P. Management of eclampsia in the accident and emergency department. Emerg. Med. J. 2000; 17:7-11.
 Russell JA et al. Vasopressin versus norepinephrine infusion in patients with septic shock. NEJM 2008; 358(9):877-87.
 Sabatine MS et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. NEJM 2005; 352(12):1179-89.
 Stiell IG et al. The Canadian CT Head Rule for patients with minor head injury. Lancet 2001; 357(9266):1391-6.
 Stiell IG et al. The Canadian C-spine rule for radiography in alert and stable trauma patients. JAMA 2001; 286(15):1841-8.
 Varon J, Marik P. The Diagnosis and management of hypertensive crises. Chest. 2000; 118(1):214-27.
 Vidt DG. Emergency room management of hypertensive urgencies and emergencies. J Clin Hypertens, 2001; 3(3):158-64.
 Warden C et al. Evaluation and management of febrile seizures in the out-of-hospital and emergency department settings. Ann Emerg Med. 2003; 41:215-222
 Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the simpliRED d-dimer. Thromb Haemost. 2000; 83: 416-20.
 Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: Management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model. Ann Int Med. 2000; 135: 98-107.

Rupal Shah, Adil Shamji and Vithika Sivabalasundaram, chapter editors

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ADH and **oxytocin** are synthesized by the hypothalamus. They are transported via neurons to the posterior pituitary and are subsequently secreted into the systemic circulation from this location.



GENERAL FUNCTION OF ORGANS

The Hypothalamic-Pituitary Axis

Information about cortical inputs, automatic function, environmental cues (light, temp) and peripheral hormonal feedback is synthesized at the coordinating centre of the endocrine system, the hypothalamus. The hypothalamus then sends signals to the pituitary to release hormones to affect the thyroid, adrenals, gonads, growth, milk production and water balance.

Anatomy ↔ Function

Hypothalamic hormones: small peptides, no binding protein → rapid degradation
High [] in pituitary-portal blood system
Low [] in peripheral circulation
Proximity of axis preserves the pulsatile output signals from the hypothalamic neurons.

Thyroid

Thyroid hormone is critical to 1) brain and somatic development in fetus and infants, 2) metabolic activity in adults, and 3) function of virtually every organ system.

Adrenal

Each gland, 6-8g, has 1) a cortex with 3 layers that act like independent organs (zona glomerulosa → aldosterone, fasciculata → cortisol, reticularis → androgen and estrogen precursors), and 2) a medulla that acts like a sympathetic ganglion to store/synthesize adrenaline and noradrenaline.

Gonads

Bifunctional: sex steroid synthesis and gamete production
Sex steroids controls sexuality and affect metabolic and brain functions

Parathyroid

Synthesize and secrete PTH, a principle regulator of ECF Ca, regulated by [Ca], [Mg] and 1,25(OH)₂D (active metabolite of Vit-D).

Pancreas

Endocrine islet cells produce insulin: oppose glucose production (glycogenolysis, gluconeogenesis), increase glucose uptake into muscle, liver and fat. Glucagon, epinephrine, cortisol, and GH are counter regulatory.

Basic Anatomy Review

Major Endocrine Organs

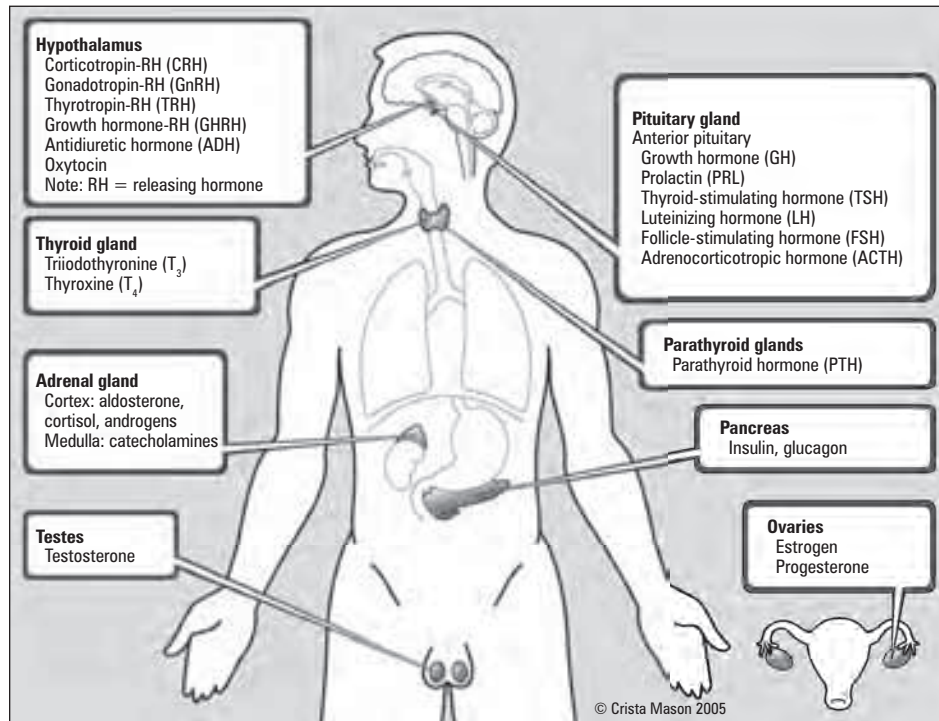


Figure 1. Endocrine System

Dyslipidemias

Definition

- metabolic disorders characterized by elevations of fasting plasma cholesterol, and/or triglycerides (TG), and/or low HDL

Overview of Lipid Transport

- lipoproteins are spherical complexes that consist of a lipid core surrounded by a shell of water-soluble proteins and phospholipids
- lipoproteins transport lipids within the body
- apolipoproteins serve as enzyme co-factors and stabilize the lipoprotein micelle

Table 1. Lipoproteins

Lipoprotein	Apolipoproteins	Function
Exogenous pathway		
Chylomicron	B-48, C, E, A-I, A-II, A-IV	• Transports dietary TG from gut to adipose tissue and muscle
Endogenous Pathway		
VLDL	B-100, C, E	• Transports hepatic synthesized TG from liver to adipose tissue and muscle
IDL	B-100, E	• Product of hydrolysis of VLDL by lipoprotein lipase resulting in depletion of TG core • Enriched in cholesterol esters
LDL	B-100	• Formed by further removal of residual TG from IDL core by hepatic lipase resulting in greater enriched particles with cholesterol esters • Transports cholesterol from liver to peripheral tissues (gonads, adrenals)
HDL	A-I, A-II, C, E	• Transports cholesterol from peripheral tissues to liver • Acts as a reservoir for apolipoproteins

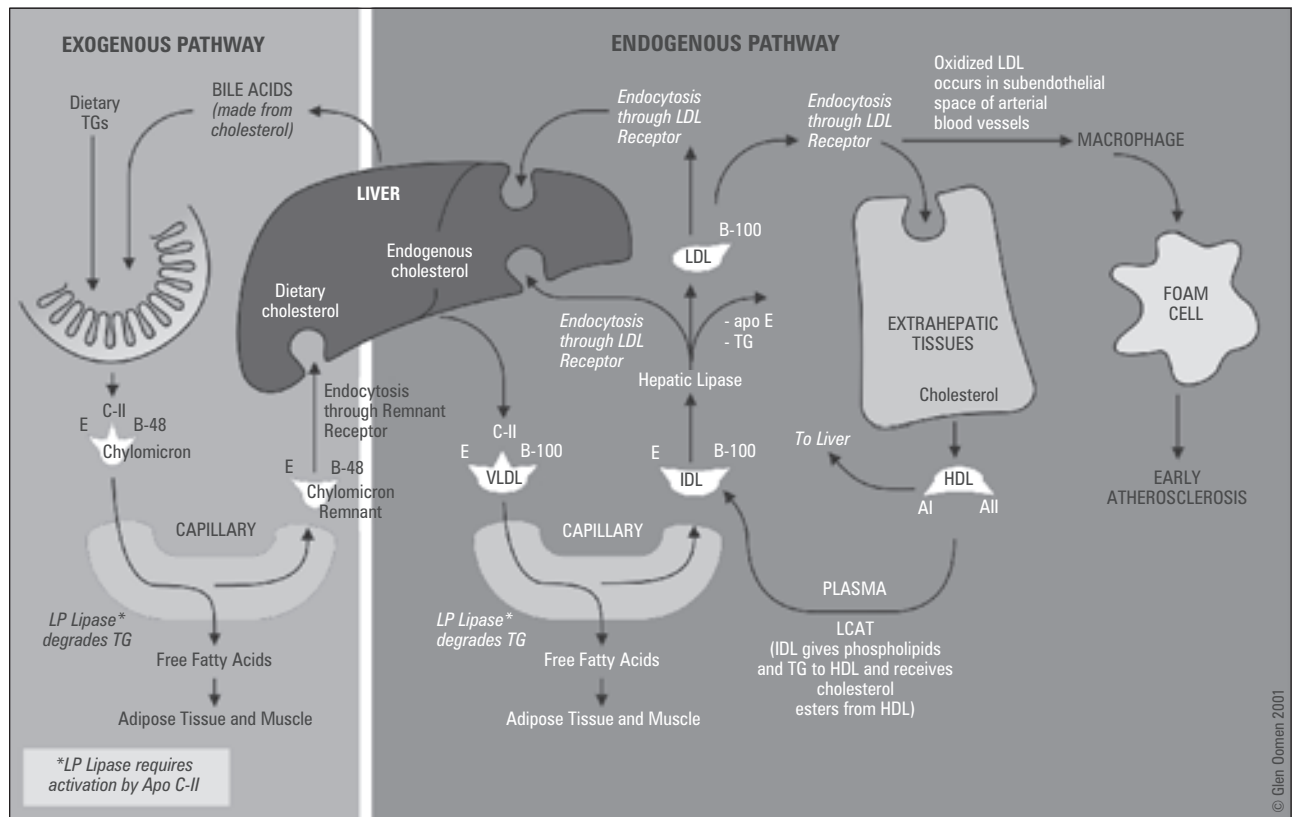


Figure 2. Exogenous and Endogenous Biosynthetic Lipid Pathways

Hypercholesterolemia

PRIMARY HYPERCHOLESTEROLEMIA

Table 2. The Primary Hypercholesterolemias

Hypercholesterolemia	Etiology/Pathophysiology	Labs	Clinical Presentation	Treatment
Familial Hypercholesterolemia (Frederickson Type IIa)	<ul style="list-style-type: none"> 1/500 in US population Autosomal dominant with high penetrance Defect in the normal LDL receptor on cell membranes 	↑ LDL ↑ TC	<ul style="list-style-type: none"> Tendinous xanthomatosis (achilles, patellar, and extensor tendons of hand) Arcus corneae Xanthelasma Heterozygotes: premature CAD, 50% risk of MI in men by age 30 Homozygotes: manifest CAD and other vascular disease early in childhood and can be fatal (<20 y) if untreated 	<ul style="list-style-type: none"> Heterozygotes: improvement of LDL with dual combination of HMG CoA reductase inhibitors, niacin, or bile acid sequestrants Homozygotes: partial control with portacaval shunt or LDL apheresis in conjunction with niacin; large dose atorvastatin is modestly effective
Polygenic Hypercholesterolemia	<ul style="list-style-type: none"> Most common Few mild inherited defects in cholesterol metabolism 	↑ TC ↑ LDL	<ul style="list-style-type: none"> Asymptomatic until vascular disease develops No xanthomata 	<ul style="list-style-type: none"> HMG CoA reductase inhibitors, bile acid sequestrant, niacin

SECONDARY HYPERCHOLESTEROLEMIA

Etiology

- diet
- anorexia nervosa
- hypothyroidism
- cholestatic liver disease (e.g. primary biliary cirrhosis)
- nephrotic disease
- monoclonal gammopathy
- drugs (cyclosporin, diuretics, carbamazepine)

Hypertriglyceridemia (Elevated TG)

PRIMARY HYPERTRIGLYCERIDEMIA

Table 3. The Primary Hypertriglyceridemias

Hypertriglyceridemia	Etiology/Pathophysiology	Labs	Clinical Presentation	Treatment
Familial Lipoprotein Lipase deficiency (Frederickson Type I)	<ul style="list-style-type: none"> Autosomal recessive deficiency of lipoprotein lipase or its cofactor 	↑ TG ↑ Chylomicrons Moderate ↑ in VLDL	<ul style="list-style-type: none"> Hepatosplenomegaly Splenic infarct Anemia, granulocytopenia, thrombocytopenia 2° to hypersplenism Pancreatitis Lipemia retinalis Eruptive xanthomata 	<ul style="list-style-type: none"> Decrease dietary fat intake to <10% of total calories
Familial Hypertriglyceridemia (Frederickson Type IV)	<ul style="list-style-type: none"> Several genetic defects resulting in ↑ hepatic VLDL synthesis or ↓ removal of VLDL 	↑ TG ↑ VLDL	<ul style="list-style-type: none"> Eruptive xanthomata Lipemia retinalis Recurrent epigastric pain Premature CAD Early adulthood develop syndrome of obesity, hypertriglyceridemia, hyperinsulinemia and hyperuricemia 	<ul style="list-style-type: none"> Decrease dietary fat intake Abstain from EtOH Fibrates or niacin

SECONDARY HYPERTRIGLYCERIDEMIA

Etiology

- obesity/metabolic syndrome
- alcohol
- diabetes mellitus
- drugs (corticosteroids, estrogen, hydrochlorothiazide, retinoic acid, beta-blockers without intrinsic sympathomimetic action (ISA), anti-retroviral drugs)
- chronic liver failure
- hepatitis
- polyclonal and monoclonal hypergammaglobulinemia
- glycogen storage disease
- hypothyroidism
- hypopituitarism
- acromegaly

Combined Hyperlipidemia

Table 4. Primary Combined Hyperlipidemias

Hyperlipidemia	Etiology/Pathophysiology	Labs	Clinical Presentation	Treatment
Familial Combined Hyperlipidemia (Frederickson Type IIb)	<ul style="list-style-type: none"> Most common form of hyperlipidemia Over-population of VLDL and associated ↑ LDL 2° to excess hepatic synthesis of apolipoprotein B Autosomal dominant 	↑ TC + TG ↑ VLDL ↑ LDL	<ul style="list-style-type: none"> Xanthelasma CAD and other vascular disease 	<ul style="list-style-type: none"> Weight reduction Decrease fat, cholesterol, and EtOH in diet Niacin, fibrates HMG CoA reductase inhibitors
Dysbetalipoproteinemia (Frederickson Type III)	<ul style="list-style-type: none"> Abnormal apolipoprotein E 	↑ TC + TG ↑ VLDL ↑ IDL	<ul style="list-style-type: none"> Tuberous, eruptive, planar xanthomata Impaired glucose tolerance CAD and PVD 	<ul style="list-style-type: none"> Weight reduction Decrease fat, cholesterol, and EtOH in diet Niacin, fibrates HMG CoA reductase inhibitors

Dyslipidemia and the Risk for CAD

- increased LDL is a major risk factor for atherosclerosis and CAD
- increased HDL is associated with decreased cardiovascular disease and mortality
- hypertriglyceridemia is an independent risk factor for CAD in people with diabetes mellitus and in postmenopausal women

Screening

- screen men over age 40, women over age 50 or postmenopausal
- if following risk factors present, screen at any age:
 - diabetes
 - cigarette smoking
 - hypertension (sBP >140, dBP >90)
 - obesity (BMI >27 kg/m²)
 - family history of premature coronary artery disease
 - clinical signs of hyperlipidemia (xanthelasma, xanthoma, arcus corneae)
 - evidence of atherosclerosis
 - rheumatoid arthritis, systemic lupus erythematosus, psoriasis
 - HIV infection on highly active antiretroviral therapy
 - chronic kidney disease (estimated GFR <60 ml/min/1.73 m²)
 - erectile dysfunction
- screen children with a family history of hypercholesterolemia or chylomicronemia

Factors Affecting Risk Assessment

- metabolic syndrome
- apolipoprotein B (apoB):
 - each atherogenic particle [VLDL, IDL, LDL and lipoprotein(a)] contains one molecule of apoB
 - serum [apoB] reflects the total number of particles and may be useful in assessing cardiovascular risk and adequacy of treatment in high risk patients and those with metabolic syndrome

Table 5. Optimal Target Levels of Apolipoprotein B by Risk Group*

	High	Moderate	Low
Target apoB levels (g/L)	<0.85	<1.05	<1.2

*Risk Stratification by Framingham Risk Score. See *Family Medicine*, FM7

- C-reactive protein (CRP) levels:
 - highly sensitive acute phase reactant
 - may be clinically useful in identifying those at a higher risk of cardiovascular disease than predicted by the global risk assessment

Treatment of Dyslipidemias

Approach to Treatment

For clinical guidelines see *Can J Cardiol* 2009; 25(10):567-579.

- estimate 10-year risk of CAD using Framingham model (see *Family Medicine*, FM6)
- establish treatment targets according to level of risk (see Table 6)

Table 6. Target LDL by Risk Group

Level of Risk	10-year Risk of CAD	Target LDL (mmol/L)	(mg/dL)	Target TC/HDL	Alternate
High	≥20%	<2.0	<78 mg/dL	<4	apoB <0.80 g/L
Moderate	10-19%	<3.5	<136.5 mg/dL	<5	apoB <0.80 g/L
Low	<10%	<5.0	<195 mg/dL	<6	

Table 7. Treatment of Hypercholesterolemia and Hypertriglyceridemia

Treatment of Hypercholesterolemia	Treatment of Hypertriglyceridemia
<ul style="list-style-type: none"> • Conservative: 4-6 month trial unless high risk group, in which case medical treatment should start immediately <ul style="list-style-type: none"> ▪ Diet <ul style="list-style-type: none"> • Decrease fat: <30% calories • Decrease saturated fat: <10% calories • Decrease cholesterol: <300 mg/day • Increase fibre: >25-35 g/day ▪ Decrease alcohol intake ▪ Smoking cessation ▪ Aerobic exercise: 30-60 minutes/day, 4-7 times/week ▪ Weight loss: target body mass index (BMI) <25 • Medical <ul style="list-style-type: none"> ▪ HMG-CoA reductase inhibitors, ezetimibe, bile acid sequestrants, niacin (see <i>Common Medications</i> section) 	<ul style="list-style-type: none"> • Conservative: 4-6 month trial <ul style="list-style-type: none"> ▪ Diet <ul style="list-style-type: none"> • Decrease fat and simple carbohydrates • Increase omega-3 fatty acids ▪ Control blood sugars ▪ Decrease alcohol intake ▪ Smoking cessation ▪ Aerobic exercise: 30-60 minutes/day, 4-7 times/week ▪ Target body mass index (BMI) <25 • Medical: fibrates, niacin (see <i>Common Medications</i> section) <ul style="list-style-type: none"> ▪ Indications: <ul style="list-style-type: none"> • Failed conservative measures • TG >10 mmol/L (885 mg/dL) to prevent pancreatitis • Combined hyperlipidemia



Non-traditional Positive Risk Factors

- ↑ Apo-B (apolipoprotein B)
- ↓ Apo A-1 (apolipoprotein A-1)
- Small dense LDL
- ↑ fibrinogen
- ↑ PAI-1
- ↑ IL-6 (interleukin 6)
- ↑ TNF (tumour necrosis factor)
- ↑ CRP (c-reactive protein)
- ↓ adiponectin
- ↑ homocysteine



Treatment Effect

Each 1.0 mmol/L decrease in LDL corresponds to 20-25% relative risk reduction in cardiovascular disease.



For Statin Follow-Up

- Lipids and liver enzymes every 4-6 months or if patient complains of jaundice, RUQ pain, dark urine
- CK at baseline and if patient complains of myalgia
- D/C statin if CK >10x upper limit of normal

Intensive Lipid Lowering in CAD: TNT

NEJM 2005; 352(14):1425-35

Study: Multicentre, randomized, double-blinded trial with median follow-up of 4.9 years.

Patients: 10,001 patients with CAD and LDLC <3.4.

Intervention: 80 mg versus 10 mg atorvastatin daily.

Main outcomes: Death from CAD, MI, cardiac arrest, or stroke.

Results: A primary event occurred in 8.7% of the patients receiving intensive therapy, compared to 10.9% of patients receiving standard therapy (RR 0.78, p<0.001). There was no difference in overall mortality. Incidence of persistent transaminase elevations was higher in the intensive therapy group (1.2% versus 0.2%, p<0.001).

Conclusion: Intensive statin therapy is associated with lower rates of CAD events than standard therapy, but also a higher rate of transaminase elevation.

Simvastatin to Lower CAD Risk – The Heart Protection Study

Lancet 2002; 360:7-22

Study: Randomized, double-blind, placebo-controlled trial (median follow-up 5.0 years).

Patients: 20,536 patients with coronary disease, other occlusive arterial disease, or diabetes (aged 40-80 years) who had a total cholesterol level of 3.5mmol/L.

Intervention: Simvastatin 40 mg/day or placebo.

Main Outcomes: Mortality, fatal or non-fatal vascular events.

Results: The use of simvastatin significantly decreased total mortality (12.9 vs. 14.7, p=0.0003) and the first event rate of any cardiovascular event by 25% (p<0.0001).

Conclusion: Treatment with simvastatin improved survival and cardiovascular outcomes in high-risk CAD patients.

Disorders of Glucose Metabolism

Overview of Glucose Regulation

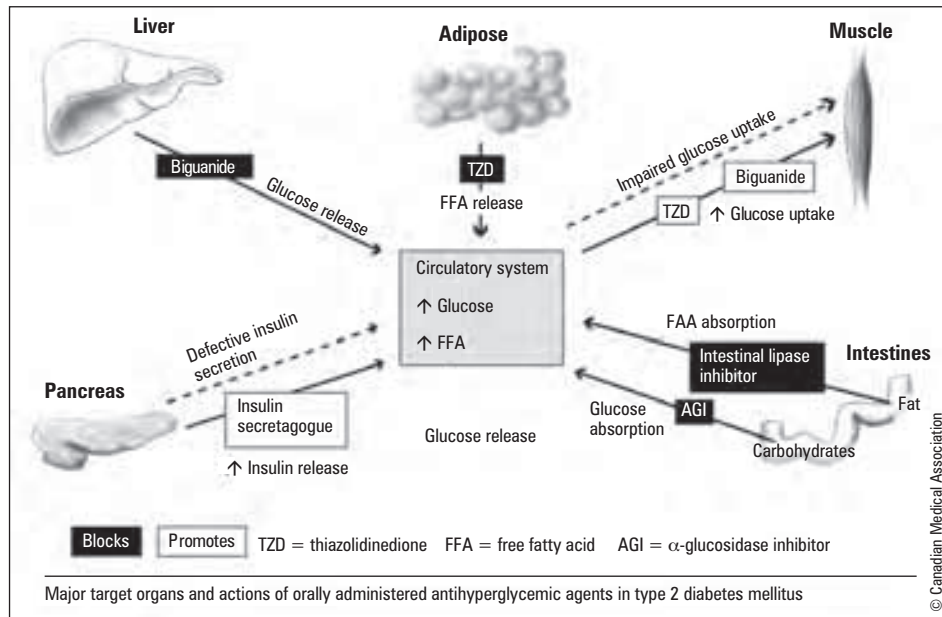


Figure 3. Antihyperglycemic Agents

Pre-Diabetes (Impaired Glucose Tolerance/ Impaired Fasting Glucose)

- 1-5% per year go on to develop diabetes mellitus
- 50-80% revert to normal glucose tolerance
- weight loss may improve glucose tolerance
- increased risk of developing macrovascular complications
- lifestyle modifications decrease progression to DM by 51%

Diagnostic Criteria

- impaired fasting glucose (IFG): fasting blood glucose (FBG) 6.1-6.9 mmol/L (110-125 mg/dL)
- impaired glucose tolerance (IGT): 2h 75 g oral glucose tolerance test (OGTT) 7.8-11.0 mmol/L (140-200 mg/dL)

Diabetes Mellitus (DM)

Definition

- syndrome of disordered metabolism and inappropriate hyperglycemia secondary to an absolute/ relative deficiency of insulin, or a reduction in biological effectiveness of insulin, or both

Diagnostic Criteria

- any one of the following is diagnostic:
 - presence of classic symptoms of DM (polyuria, polydipsia, polyphagia, weight loss, blurry vision, nocturia, ketonuria) PLUS random blood glucose (BG) ≥ 11.1 mmol/L (200 mg/dL)
 - FBG ≥ 7.0 mmol/L (126 mg/dL)
 - 2h 75 g OGTT ≥ 11.1 mmol/L (200 mg/dL)
 - HbA1C $\geq 6.5\%$ (American Diabetes Association Guidelines, Jan 2010)

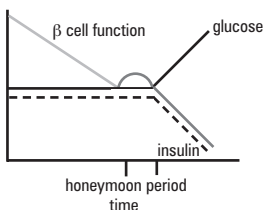
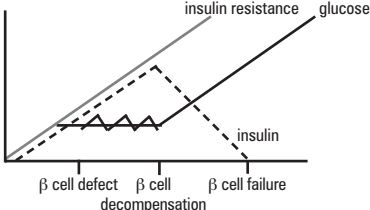
Etiology and Pathophysiology

Table 8. Etiologic Classification of Diabetes Mellitus

- I. **Type 1 diabetes** (immune-mediated beta cell destruction, usually leading to absolute insulin deficiency)
- II. **Type 2 diabetes** (ranges from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance 2° to beta cell dysfunction)
- III. **Other specific causes of diabetes:**
 - a. Genetic defects of beta cell function (e.g. MODY – Maturity-Onset Diabetes of the Young) or insulin action
 - b. Diseases of the exocrine pancreas:
 - Pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis (“bronze diabetes”)
 - c. Endocrinopathies:
 - Acromegaly, Cushing’s syndrome, glucagonoma, pheochromocytoma, hyperthyroidism
 - d. Drug-induced:
 - Glucocorticoids, thyroid hormone, beta-adrenergic agonists, thiazides, phenytoin, clozapine
 - e. Infections:
 - Congenital rubella, CMV, coxsackie
 - f. Genetic syndromes associated with diabetes:
 - Down’s syndrome, Klinefelter’s syndrome, Turner’s syndrome

IV. Gestational Diabetes Mellitus

Table 9. Comparison of Type 1 and Type 2 Diabetes Mellitus

	Type 1	Type 2
Onset	<ul style="list-style-type: none"> Usually <30 years of age 	<ul style="list-style-type: none"> Usually >40 years of age Increasing incidence in pediatric population 2° to obesity
Epidemiology	<ul style="list-style-type: none"> More common in Caucasians Rare in Asians, Hispanics, Aboriginals, and Blacks Accounts for 5-10% of all DM 	<ul style="list-style-type: none"> More common in Blacks, Hispanics, Aboriginals, Asians Accounts for >90% of all DM
Etiology	<ul style="list-style-type: none"> Autoimmune 	<ul style="list-style-type: none"> Complex and multifactorial
Genetics	<ul style="list-style-type: none"> Monozygotic twin concordance is 30-40% Associated with HLA class II DR3 and DR4, with either allele present in up to 95% of Type 1 DM Certain DQ alleles also confer a risk 	<ul style="list-style-type: none"> Greater heritability than Type 1 DM Monozygotic twin concordance is 70-90% Polygenic Non-HLA associated
Pathophysiology	<ul style="list-style-type: none"> Synergistic effects of genetic, immune, and environmental factors that cause beta cell destruction resulting in impaired insulin secretion Autoimmune process is believed to be triggered by environmental factors (e.g. viruses, bovine milk protein, urea compounds) Pancreatic cells are infiltrated with lymphocytes resulting in islet cell destruction 80% of beta cell mass is destroyed before features of diabetes present 	<ul style="list-style-type: none"> Impaired insulin secretion, peripheral insulin resistance (likely due to receptor and post receptor abnormality), and excess hepatic glucose production
Natural history	 <ul style="list-style-type: none"> After initial presentation, honeymoon period often occurs where glycemic control can be achieved with little or no insulin treatment as residual cells are still able to produce insulin Once these cells are destroyed, there is complete insulin deficiency 	 <ul style="list-style-type: none"> Early on, glucose tolerance remains normal despite insulin resistance as beta cells compensate with increased insulin production As insulin resistance and compensatory hyperinsulinism continue, the beta cells are unable to maintain the hyperinsulinemic state which results in glucose intolerance and diabetes
Circulating autoantibodies	<ul style="list-style-type: none"> Islet cell Ab present in up to 60-85% Most common islet cell Ab is against glutamic acid decarboxylase (GAD) Up to 60% have Ab against insulin 	<ul style="list-style-type: none"> <10%

Three-year Efficacy of Complex Insulin Regimens in Type 2 Diabetes: 4T Trial

NEJM 2009; 361:1736-47

Study: Randomized, unblinded trial with 3 years of follow-up.

Population: 708 patients with type 2 diabetes, not on insulin or thiazolidinedione therapy, on maximal metformin and sulfonylurea therapy.

Intervention: Thrice-daily prandial insulin aspart, versus twice-daily biphasic insulin aspart, versus once-daily basal insulin detemir. Sulfonylurea therapy was replaced with a secondary insulin regime specific to each arm if there was persistent hyperglycemia.

Primary Outcome: 3-year hemoglobin HgA1c.

Results: Significant difference in rates of patient withdrawal from the study: 5.1% biphasic, 11.7% prandial, 8.5% basal regimens ($p=0.04$). There were no significant differences in median HbA1C levels between all three arms from year 1 to 3. A smaller proportion of patients reached HbA1C <6.5% or <7.0% in the biphasic arm. The basal arm had least weight gain and least weight circumference increase, but highest rate of secondary insulin requirement. The basal arm had fewest severe hypoglycemic events per patient year, while the biphasic had the most serious adverse effects.

Conclusion: Basal insulin regime provides the best glycemic control over a 3-year study; with better HbA1C control, fewer hypoglycemic events, and less weight gain.

Blood Glucose Control in Type 2 DM – UKPDS 33

Lancet 1998; 352:837-53

Study: Randomized controlled trial (mean follow-up 10 years).

Patients: 3867 patients with newly diagnosed Type 2 DM (mean age 53 y, 61% men, 81% white, mean fasting plasma glucose (FPG) 6.1-15.0 mmol/L). Exclusions included severe cardiovascular disease, renal disease, retinopathy, and others.

Intervention: Intensive treatment with a sulfonylurea or insulin (target FPG <6 mmol/L) vs. conventional treatment with diet alone (target FPG <15 mmol/L without hyperglycemic symptoms).

Main outcomes: Diabetes-related endpoints (MI, angina, heart failure, stroke, renal failure, amputation, retinopathy, blindness, death from hyperglycemia or hypoglycemia), diabetes-related death, and all-cause mortality.

Results: Patients allocated to intensive treatment had lower median HbA1C levels ($p<0.001$).

Outcome	RRR % (p value)
Diabetes-related endpoint	12 (0.029)
Diabetes-related death	10 (0.34)
All-cause mortality	6 (0.44)

Patients allocated to intensive therapy had more hypoglycemic episodes and greater weight gain.

Conclusion: Intensive blood glucose control reduces microvascular, but not macrovascular complications in Type 2 DM.

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 DM: The ADVANCE Trial

NEJM 2008; 358:2560-72

Study: Multicentre, randomized, controlled trial.

Patients: 11,140 patients with Type 2 DM and risk factors for vascular disease.

Intervention: Intensive glucose control (HbA1C $\leq 6.5\%$) versus standard glucose control (determined by local guidelines).

Primary Outcomes: Composite macrovascular (death from cardiovascular cause, nonfatal MI, nonfatal stroke) and microvascular events (nephropathy, retinopathy).

Results: The incidence of the composite primary outcome was lower in the intensive glucose control arm. Individually, there was no difference in macrovascular events or all-cause mortality, but there was a lower incidence of microvascular events, nephropathy, new-onset microalbuminuria, and macroalbuminuria in the intensive glucose control arm. All-cause hospitalization, hypoglycemia-related hospitalization, and severe hypoglycemia occurred more frequently in the intensive glucose control arm.

Conclusions: Intensive glucose control can improve microvascular outcomes, especially nephropathy, but does not impact macrovascular events or mortality, and has greater incidence of hypoglycemic adverse events in patients with Type 2 DM.

Table 9. Comparison of Type 1 and Type 2 Diabetes Mellitus (continued)

	Type 1	Type 2
Risk Factors	<ul style="list-style-type: none"> Personal history of other autoimmune diseases including Graves', myasthenia gravis, autoimmune thyroid disease, celiac disease and pernicious anemia 	<ul style="list-style-type: none"> Age >40 y Abdominal obesity/overweight First-degree relative with DM Race/ethnicity (Black, Aboriginal, Hispanic, Asian-American, Pacific Islander) History of IGT or IFG HTN Dyslipidemia PCOS Gestational DM Schizophrenia Fatty liver Hyperuricemia
Body Habitus	<ul style="list-style-type: none"> Normal to wasted 	<ul style="list-style-type: none"> Typically overweight with increased central obesity
Treatment	<ul style="list-style-type: none"> Insulin 	<ul style="list-style-type: none"> Lifestyle modification Oral antihyperglycemic agents Insulin therapy
Acute Complication	<ul style="list-style-type: none"> Diabetic ketoacidosis 	<ul style="list-style-type: none"> Hyperosmolar nonketotic (HONK) hyperglycemic state
Screening	<ul style="list-style-type: none"> Subclinical prodrome can be detected in first and second-degree relatives of those with Type 1 DM by the presence of pancreatic islet autoantibodies 	<ul style="list-style-type: none"> Screen individuals with risk factors (see above)

Treatment of Diabetes

Glycemic Targets

- HbA1C reflects glycemic control over 3 months and is a measure of patient's long-term diabetes control
- American Diabetes Association (ADA) suggests HbA1C $<7.0\%$, whereas American Association of Clinical Endocrinologists (AACE) suggests $<6.5\%$
- Canadian Diabetes Association (CDA) guidelines recommend target $<7.0\%$
- there may be harm associated with strategy to target HbA1C $<6.0\%$ in certain patients with Type 2 DM (see EBM box re: ACCORD trial, E9)

Canadian Diabetes Guidelines 2008

	Target	Optimal
HbA1C	$<7.0\%$	$<6.0\%$
Fasting plasma glucose	4-7 mmol/L (72-126 mg/dL)	4-6 mmol/L (72-108 mg/dL)
2h post prandial glucose	5-10 mmol/L (90-180 mg/dL)	5-8 mmol/L (90-144 mg/dL)
Lipids	As per high or moderate risk group	Same
Blood pressure	$<130/80$	Same

A target A1C of 6.5% may be considered in some patients with type 2 diabetes but this should be balanced against the risk of hypoglycemia.

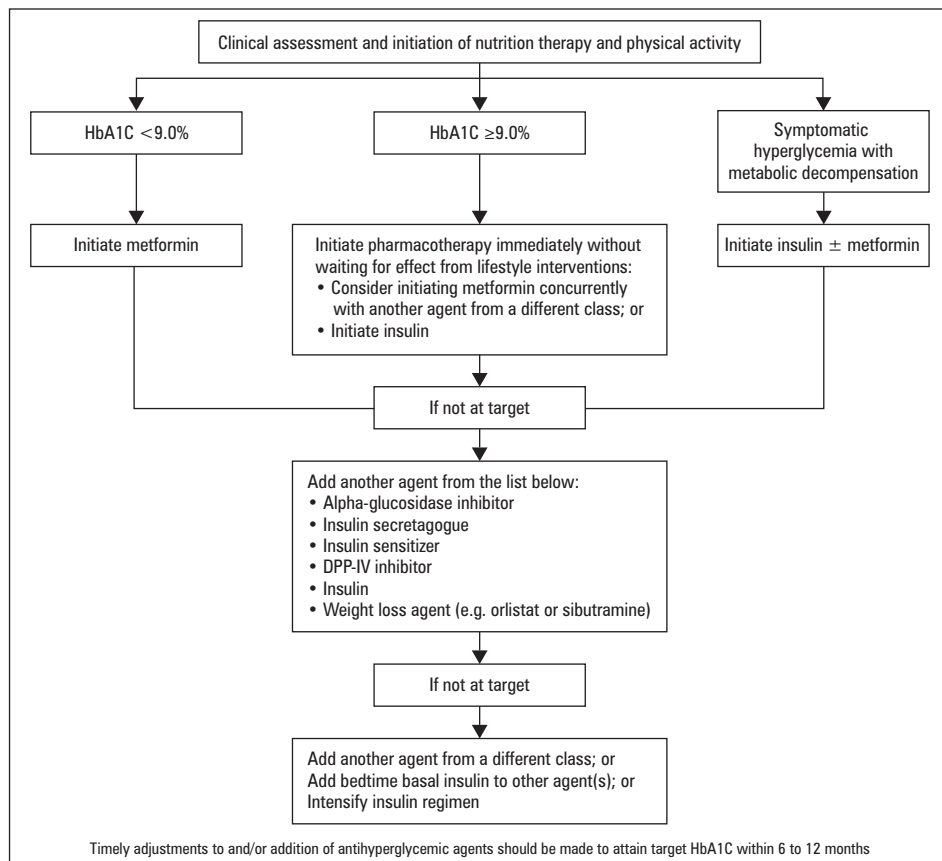


Figure 4. Approach to Treatment of Hyperglycemia in Type 2 DM

Adapted from *Can J Diabetes* 2008; 32(suppl1):S56

Diet

- daily carbohydrate intake 50-55% of energy, protein 15-20% of energy and fat <30% of energy
- intake of both saturated and polyunsaturated fats <10% of total calories each
- limit sodium, alcohol and caffeine intake
- Type 1: carbohydrate counting is used to titrate insulin regimen
- Type 2: weight reduction

Lifestyle

- regular physical exercise to improve insulin sensitivity, lower lipid concentrations and control blood pressure
- smoking cessation

Medical Treatment: Oral Antihyperglycemic Agents (Type 2 DM)

- initiate oral antihyperglycemic therapy within 2-3 months if lifestyle management does not result in glycemic control
- if HbA1C >9.0%, initiate pharmacologic therapy immediately and consider combination oral therapy or insulin immediately
- see *Common Medications*, E51 for details on antihyperglycemic agents

Medical Treatment: Insulin (Figure 5)

- used for Type 1 DM, may be used in Type 2 DM at any point in treatment
- routes of administration: subcutaneous injections, continuous subcutaneous insulin infusion pump, IV infusion (regular insulin only)
- bolus insulins: short-acting (Humulin R, Novolin Toronto), rapid-acting analogue (Apidra, Humalog, Novorapid)
- basal insulins: intermediate-acting (Humulin N, Novolin NPH), long-acting analogue (Lantus, Levemir)
- premixed insulins (%R and %NPH) 10/90, 20/80, 30/70, 40/60, 50/50; analogues (Humalog Mix25®, Humalog Mix50®, Novomix 30®)
- estimated total daily insulin requirement: 0.5-0.7 units/kg

Table 10. Available Insulin Formulations

Insulin Type (trade name)	Onset	Peak	Duration
Prandial (bolus) insulins			
Rapid-acting insulin analogues			
• Insulin aspart (NovoRapid)	10-15 min	1-1.5 h	3-5 h
• Insulin lispro (Humalog)	10-15 min	1-2 h	3.5-4.75 h
• Insulin glulisine (Apidra)	10-15 min	1-1.5 h	3-5 h
Short-acting insulins			
• Humulin R	30 min	2-3 h	6.5 h
• Novolin Toronto			
Inhaled insulin	10-20 min	2 h	6 h
Basal insulins			
Intermediate-acting			
• Humulin N	1-3 h	5-8 h	Up to 18 h
• Novolin NPH			
Long-acting basal insulin analogues			
Insulin detemir (Levemir)	90 min	Not applicable	Up to 24 h (glargine 24 h, detemir 16-24 h)
Insulin glargine (Lantus)			
Pre-mixed insulins			
Premixed regular insulin – NPH			
• Humulin 30/70	A single vial or cartridge contains a fixed ratio of insulin (% of rapid acting or short-acting insulin to % of intermediate-acting insulin)		
• Novolin 30/70, 40/60, 50/50			
Premixed insulin analogues			
• Biphasic insulin aspart (NovoMix 30)			
• Insulin lispro/lispro protamine			
• Humalog Mix25 and Mix50			

Effects of Intensive Glucose Lowering in Type 2 DM: The ACCORD Trial

NEJM 2008; 358:2545-59

Study: Multicentre, randomized, controlled trial.

Patients: 10,251 patients (mean age 62.2) with Type 2 DM, and cardiovascular risk factors.

Intervention: Intensive therapy targeting a HbA1C level of less than 6.0% or standard therapy targeting 7.0 to 7.9%.

Outcomes: First occurrence of nonfatal MI, nonfatal stroke, or death from CV causes.

Results: The intensive therapy arm was stopped early (3.5 yrs vs. 5.6 yrs planned) due to evidence of increased mortality. There was no difference in primary outcome for either study arm. There was a significant increase in all-cause mortality, CV-cause mortality, nonfatal MI, and all congestive heart failure in the intensive therapy group. There were increased rates of all hypoglycemic events, any nonhypoglycemic serious adverse event, fluid retention, and weight gain >10 kg, but lower systolic and diastolic blood pressure in the intensive therapy group. There was an increased incidence of elevated ALT (>3 times upper limit) and ACE drug use in the standard therapy group.

Conclusions: Intensive glucose lowering therapy in Type 2 DM does not improve clinic outcomes and actually increases the risk of mortality with more adverse events compared to standard therapy. Additional research is required to discern the cause.

Effects of Intensive Blood Pressure Control in Type 2 DM: The ACCORD Trial

NEJM 2010; 362:1575-85

Study: RCT, unblinded with 4.7 years of mean follow-up.

Population: 4,733 patients with type 2 diabetes, risk factors for cardiovascular (CV) disease, systolic blood pressure (sBP) between 130-180 mmHg.

Intervention: sBP control less than 120 mmHg (intensive) or 140 mmHg (standard).

Primary Outcomes: Major CV event (composite nonfatal myocardial infarction, nonfatal stroke, or CV-related death).

Results: Mean number of medications at 1 year for intensive therapy was 3.4 (95% CI, 3.4-3.5) versus 2.1 (95% CI, 2.1-2.2) for standard therapy. There was a significant increase in all serious adverse events in the intensive treatment arm (3.3% vs. 1.27%, $p < 0.001$); especially bradycardia or arrhythmia (0.5% vs. 0.13%, $p = 0.02$) and hyperkalemia (0.4% vs. 0.04%, $p = 0.01$). There was no significant difference in primary outcomes in the two study arms, or all-cause mortality. There was a significant reduction in any stroke (0.32%/yr vs. 0.53%/yr, $p = 0.01$) and nonfatal stroke incidences (0.30%/yr vs. 0.47%/yr, $p = 0.03$) in the intensive therapy arm.

Conclusions: Intensive BP lowering to less than 120 mmHg versus 140 mmHg in patients with Type 2 DM and CV risk factors does not reduce major CV event risk reduction except for stroke events.

Effects of Combination Lipid Therapy in Type 2 DM: the ACCORD Trial

NEJM 2010; 362(18):1563-74

Study: RCT, double-blinded trial with 4.7 years of mean follow-up.

Population: 5,518 patients with type 2 diabetes.

Intervention: Statin with or without fibrate therapy.

Primary Outcome: Major cardiovascular (CV) event (composite nonfatal myocardial infarction, nonfatal stroke, or CV-related death).

Results: No significant differences primary outcome between the two arms. No difference in all myocardial infarction, all stroke, or all-cause mortality between study arms.

Conclusions: The addition of fibrate therapy to statin therapy in patients with Type 2 DM does not reduce major CV event risk.

**DPP-IV Inhibitors**

- Newer antihyperglycemic agents that inhibit the degradation of endogenous incretin hormones like GLP-1
- Stimulate insulin secretion, inhibit glucagon release from the pancreas and delay gastric emptying

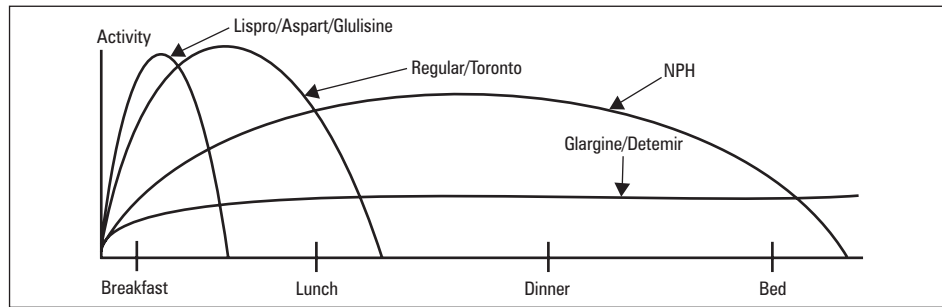


Figure 5. Duration of Activity of Different Insulins

Insulin Regimens

1. Oral agent + basal insulin (NPH, detemir, glargine) (Type 2 only)
 - start with 10 units qhs, titrate up until FBG <7.0 mmol/L (126 mg/dL)
 - continue metformin and/or insulin secretagogue
2. Twice daily injections with premixed insulin
 - insulin mixture used depends on the distribution of carbohydrates in meals but usually start with 30/70
 - estimate total daily insulin requirement then split dose into 2/3 in AM and 1/3 before supper
 - AM bolus targets pre-lunch BG and AM basal targets pre-supper BG
 - PM bolus targets bedtime BG and PM basal targets FBG
 - continue metformin and discontinue secretagogue with this regimen
 - ♦ advantages: one type of insulin, 2 injections
 - ♦ disadvantages: requires rigid meal timing and carbohydrate content; limited ability to respond to increased or decreased BG (i.e. serum glucose before breakfast next day)
3. Basal-Bolus therapy [multiple daily injections (MDI)]
 - estimate total daily insulin requirement then take 20% of this daily dose before breakfast, lunch, and dinner using regular, aspart, glulisine or lispro (total 60%)
 - the remaining 40% is given as NPH, glargine or detemir at bedtime
 - continue metformin and discontinue secretagogue with this regimen
 - ♦ advantages: flexible meal timing and carbohydrate content, ability to respond to increased or decreased BG, or planned exercise
 - ♦ disadvantages: multiple injections

Table 11. Titrating Insulin Doses

Insulin Regime	Morning Blood Glucose	Lunch Blood Glucose	Dinner Blood Glucose	Bedtime Blood Glucose	Adjustments*
Twice Daily/MDI	Increased				Increase Evening I/L
Twice Daily/MDI		Increased			Increase Morning R/S
Twice Daily			Increased		Increase Morning I/L
MDI			Increased		Increase Lunch R/S
Twice Daily/MDI				Increased	Increase Evening R/S

* R=rapid acting, S=short-acting insulin, I= Intermediate Acting, L=Long-acting

Variable Insulin Dose Schedule ("Sliding/Supplemental/Correction Scale")

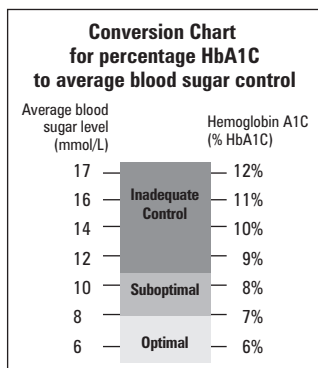
- patient takes usual doses of basal insulin but varies doses of bolus insulin based on BG reading at time of dose
- use baseline bolus insulin dose when within BG target range; add or subtract units when above or below target
- commonly used in hospital or in perioperative management of diabetes
- construction of a sliding scale for a patient on anti-hyperglycemics:
 - Correction Factor (CF) = 100/Total Daily Dose of insulin (TDD)
 - BS <4: call MD and give 15 g carbohydrates
 - BS between 4 to (7 + CF): no additional insulin
 - BS between (7 + CF) to (7 + 2CF): give one unit
 - BS between (7 + 2CF) to (7 + 3CF): give two units

Insulin Pump Therapy

- external battery-operated device provides continuous basal dose of rapid-acting insulin analogue (aspart, glulisine or lispro) through small subcutaneous catheter
- at meals, patient programs pump to deliver insulin bolus
- provides improved quality of life and flexibility
- risk of DKA if pump is inadvertently disconnected

Calculating Average Blood Sugar from HbA1C

- Average blood sugar = (HbA1C x 2) - 4



Conversion chart adapted from Nathan DM et al. The clinical information value of a glycosylated hemoglobin assay. *NEJM* 1984; 310:341-6

Acute Complications

Table 12. Acute Complications of Diabetes Mellitus: Hyperglycemic Comatose States

	Diabetic Ketoacidosis (DKA)	Hyperglycemic Hyperosmolar Nonketotic State (HONK)
Pathophysiology	<ul style="list-style-type: none"> Usually occurs in Type 1 DM Insulin deficiency with ↑ counterregulatory hormones (glucagon, cortisol, catecholamines, GH) Can occur with lack of insulin (noncompliance, poor dosage, 1st presentation) or increased stress (surgery, infection, exercise) Unrestricted hepatic glucose production → hyperglycemia → osmotic diuresis → dehydration and electrolyte disturbance → ↓ Na (pseudohyponatremia) Fat mobilization → ↑ FFA → ketoacids → metabolic acidosis Severe hyperglycemia exceeds the renal threshold for glucose and ketone reabsorption → glucosuria and ketonuria Total body K depletion but serum K may be normal or elevated 2° to shift from ICF to ECF due to lack of insulin, ↑ plasma osmolality Total body PO₄ depletion 	<ul style="list-style-type: none"> Occurs in Type 2 DM Often precipitated by sepsis, stroke, MI, CHF, renal failure, trauma, drugs (glucocorticoids, immunosuppressants, phenytoin, diuretics), dialysis, recent surgery, burns Partial or relative insulin deficiency decreases glucose utilization in muscle, fat, and liver while inducing hyperglucagonemia and hepatic glucose production Presence of a small amount of insulin prevents the development of ketosis by inhibiting lipolysis Characterized by hyperglycemia, hyperosmolality, and dehydration without ketosis More severe dehydration compared to DKA due to more gradual onset and ↑ duration of metabolic decompensation plus impaired fluid intake which is common in bedridden or elderly Volume contraction → renal insufficiency → ↑ hyperglycemia, ↑ osmolality → shift of fluid from neurons to ECF → mental obtundation and coma
Clinical Features	<ul style="list-style-type: none"> Polyuria, polydipsia, polyphagia with marked fatigue, nausea, vomiting Dehydration (orthostatic changes) LOC may be ↓ with high serum osmolality (osm >330 mmol/L) Abdominal pain Fruity smelling breath Kussmaul's respiration 	<ul style="list-style-type: none"> Onset is insidious → preceded by weakness, polyuria, polydipsia History of decreased fluid intake History of ingesting large amounts of glucose containing fluids Dehydration (orthostatic changes) ↓ LOC → lethargy, confusion, comatose Kussmaul's respiration is absent unless the underlying precipitant has also caused a metabolic acidosis
Serum	<ul style="list-style-type: none"> ↑ BG (11-55 mmol/L, 198-990 mg/dL), ↓ Na (spurious 2° to hyperglycemia → for every ↑ in BG by 10 mmol/L (180 mg/dL) there is a ↓ in Na by 3 mmol/L) Normal or ↑ K, ↓ HCO₃, ↑ BUN, ↑ Cr, ketonemia, ↓ PO₄ ↑ osmolality 	<ul style="list-style-type: none"> ↑ BG (44.4-133.2 mmol/L, 800-2400 mg/dL) In mild dehydration, may have hyponatremia (spurious 2° to hyperglycemia → for every ↑ in BG by 10 mmol/L (180 mg/dL) there is a ↓ in Na by 3 mmol/L) – if dehydration progresses, may get hypernatremia Ketosis usually absent or mild if starvation occurs ↑ osmolality
ABG	<ul style="list-style-type: none"> Metabolic acidosis with ↑ AG, possible 2° respiratory alkalosis If severe vomiting/dehydration there may be a metabolic alkalosis 	<ul style="list-style-type: none"> Metabolic acidosis absent unless underlying precipitant leads to acidosis (e.g. lactic acidosis in MI)
Urine	<ul style="list-style-type: none"> +ve for glucose and ketones 	<ul style="list-style-type: none"> -ve for ketones unless there is starvation ketosis Glycosuria
Treatment	<ul style="list-style-type: none"> Immediate resuscitation and emergency measures if patient is stuporous or comatose Monitor degree of ketoacidosis with AG, not BG or serum ketone level Rehydration: <ul style="list-style-type: none"> 1 L/h NS in first 2 hrs after 1st 2 L, 300-400 ml/h 0.45% NS once BG reaches 13.9 mmol/L (250 mg/dL) then switch to D5W to maintain BG in the range of 13.9–16.6 mmol/L (250-300 mg/dL) Insulin therapy: <ul style="list-style-type: none"> critical to resolve acidosis, not hyperglycemia use only regular insulin (R) initially load 0.15 U/kg body weight insulin R bolus maintenance 0.1 U/kg/h insulin R infusion check serum glucose hourly K replacement: <ul style="list-style-type: none"> as acidosis is corrected, hypokalemia may develop when K 3.5-5.5 mmol/L add KCL 30-40mEq/L IV fluid to keep K in the range of 3.5-5 mEq/L HCO₃: <ul style="list-style-type: none"> if pH <7.0 or if hypotension, arrhythmia, or coma is present with a pH of <7.1 give HCO₃ in 0.45% NS do not give if pH >7.1 (risk of metabolic alkalosis!) can give in case of life-threatening hyperkalemia ± mannitol (for cerebral edema) 	<ul style="list-style-type: none"> Same resuscitation and emergency measures as DKA Rehydration: <ul style="list-style-type: none"> IV fluids: 1 L/h NS initially evaluate corrected serum Na if serum Na high or normal, switch to 0.45% NS (4-14 ml/kg/h) if serum Na low, maintain NS (4-14 ml/kg/h) when serum BG reaches 13.9 mmol/L (250 mg/dL) switch to D5W K replacement: <ul style="list-style-type: none"> less severe K depletion compared to DKA if serum K <3.3 mmol/L, hold insulin and give 40 mEq/L K replacement if K is 3.3-5.4, give KCl 20-30 mEq/L IV fluid if serum K ≥5.5 mmol/L, check K every 2 h Search for precipitating event Insulin therapy: <ul style="list-style-type: none"> use only regular insulin (R) initially load 0.15 U/kg body weight insulin R bolus maintenance 0.1 U/kg/h insulin R infusion or IM check serum glucose hourly in general lower insulin requirement compared to DKA
Prognosis	<ul style="list-style-type: none"> 2-5% mortality in developed countries Serious morbidity from sepsis, respiratory complications, thromboembolic complications, and cerebral edema 	<ul style="list-style-type: none"> Overall mortality approaches 50% primarily because of the older patient population and underlying etiology



The 6 I's Precipitating DKA:

Infection
Ischemia or Infarction
Iatrogenic (glucocorticoids)
Intoxication
Insulin missed
Intra-abdominal process
(e.g. pancreatitis, cholecystitis)



All Ketonemia is Not DKA:

Consider starvation or alcohol ketosis.



Average fluid loss runs at 3-6 L in DKA, and 8-10 L in HONK.

**Laboratory Testing: Ketones**

The nitroprusside test for ketones identifies acetone and acetoacetate but does NOT detect beta-hydroxybutyrate (BHB), the ketone most frequently in excess. This has two clinical consequences:

1. Be wary of a patient with a clinical picture of DKA but negative serum or urinary ketones. These could be false negatives.
2. As DKA is treated, BHB is converted to acetone and acetoacetate. Serum or urinary ketones may therefore rise, falsely suggesting that the patient is worsening.

Effect of a Multifactorial Intervention on Mortality in Type 2 DM: The Steno-2 Study
NEJM 2008; 358:580-91

Study: Single centre, randomized, controlled trial.

Patients: Patients (n=160) with Type 2 DM and persistent microalbuminuria.

Intervention: Random assignment to receive either conventional multifactorial treatment or intensified, target-driven therapy involving a combination of medications and focused behaviour modification. Targets included a HbA1C level of <6.5%, a fasting serum total cholesterol level of <4.5 mmol/L, a fasting serum triglyceride level of <1.7 mmol/L, a systolic blood pressure of <130 mmHg, and a diastolic blood pressure of <80 mmHg. Patients were treated with blockers of the renin-angiotensin system because of their microalbuminuria, regardless of blood pressure, and received low-dose aspirin as primary prevention.

Outcomes: The primary end point in the follow-up trial was the time to death from any cause. Other endpoints examined death from cardiovascular causes and various cardiovascular events along with diabetic neuropathy, nephropathy, and retinopathy.

Results: Twenty-four patients in the intensive-therapy group died, as compared with 40 in the conventional-therapy group (hazard ratio, 0.54; 95% confidence interval [CI], 0.32 to 0.89; $P=0.02$). Intensive therapy was associated with a lower risk of death from cardiovascular causes (hazard ratio, 0.43; 95% CI, 0.19 to 0.94; $P=0.04$) and of cardiovascular events (hazard ratio, 0.41; 95% CI, 0.25 to 0.67; $P<0.001$). One patient in the intensive-therapy group had progression to end-stage renal disease, as compared with six patients in the conventional-therapy group ($P=0.04$). Fewer patients in the intensive-therapy group required retinal photocoagulation (relative risk, 0.45; 95% CI, 0.23 to 0.86; $P=0.02$).

Conclusions: In at-risk patients with Type 2 DM, intensive intervention with multiple drug combinations and behaviour modification had sustained beneficial effects with respect to vascular complications and on rates of death from any cause and from cardiovascular causes.

Macrovascular Complications

- increased risk of coronary artery disease (CAD), ischemic stroke, and peripheral vascular disease (PVD) secondary to accelerated atherosclerosis
- coronary artery disease
 - risk of MI is 3-5x higher in those with diabetes compared to age-matched controls
 - CAD is the leading cause of death in Type 2 DM
 - most patients with DM are considered as “high risk” under the risk stratification for CAD (see *Dyslipidemias*, E2)
- ischemic stroke
 - risk of stroke is approximately 2.5x higher in those with diabetes
 - level of glycemia is either a risk factor for stroke or a predictor of a poorer outcome in patients who suffer a stroke
 - HbA1C level is a significant and independent predictor of the risk of stroke
- peripheral vascular disease
 - manifested by intermittent claudication in lower extremities, intestinal angina, foot ulceration
 - risk of foot gangrene is 30x higher in those with diabetes compared to age-matched controls
 - risk of lower extremity amputation is 15x higher in those with diabetes
- treatment
 - tight blood pressure control (<130/80 mmHg)
 - tight glycemic control
 - tight low density lipoprotein (LDL) cholesterol control [LDL <2.0 mmol/L (77 mg/dL)]
 - low-dose ASA in patients with CVD or increased likelihood of CV events
 - ACE inhibitor or angiotensin receptor blocker (ARB) in high-risk patients
 - smoking cessation

Microvascular Complications

DIABETIC RETINOPATHY (see *Ophthalmology*, OP35)

Epidemiology

- Type 1 DM – 25% affected at 5 years, 100% at 20 years
- Type 2 DM – 25% affected at diagnosis, 60% at 20 years
- leading cause of blindness in North America between the ages of 20-74
- most important factor is disease duration

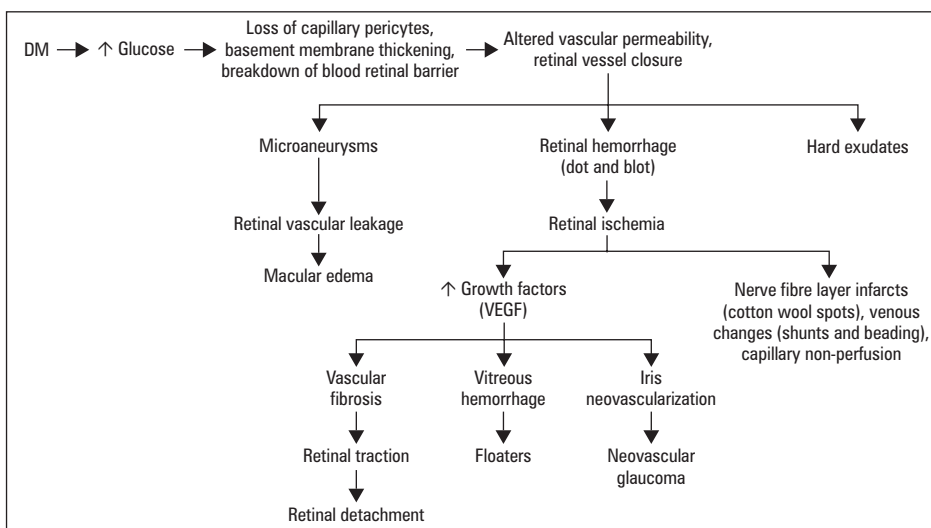


Figure 6. Pathophysiology of Diabetic Retinopathy

Clinical Features

- nonproliferative
 - asymptomatic, but if macular involvement occurs, vision may be impaired
 - microaneurysms, hard exudates, dot and blot hemorrhages
- preproliferative
 - 10-40% progress to proliferative within 1 year
 - macular edema, cotton wool spots, venous shunts and beading, intra-retinal microvascular abnormalities (IRMA)
- proliferative
 - neovascularization, fibrous scarring, vitreous hemorrhage, retinal detachment
 - great risk for loss of vision secondary to vitreous hemorrhage (floaters) and/or retinal detachment

Treatment and Prevention

- tight glycemic control (delays onset, decreases progression)
- if hypertension is present, treat aggressively
- panretinal laser photocoagulation for treatment of neovascularization
- vitrectomy
- annual follow-up visits with an eye specialist (optometrist or ophthalmologist); examination through dilated pupils whether symptomatic or not (immediate referral after diagnosis of Type 2 DM; 5 years after diagnosis of Type 1 DM)
- interval for follow-up should be tailored to severity of retinopathy

DIABETIC NEPHROPATHY (see [Nephrology](#), NP34)**Epidemiology**

- diabetes-induced renal failure is the most common cause of renal failure in North America
- 20-40% of persons with Type 1 DM (after 5-10 years) and 4-20% with Type 2 DM have progressive nephropathy

Pathophysiology

- thickening of capillary basement membrane and glomerular mesangium resulting in glomerulosclerosis and renal insufficiency
- diffuse glomerulosclerosis is more common than nodular intercapillary glomerulosclerosis (Kimmelstiel-Wilson lesions)

Screening

- random urine test for albumin to creatinine ratio (ACR) plus urine dipstick test for all Type 2 DM patients at diagnosis, then annually, and for postpubertal Type 1 DM patients with ≥ 5 years duration of DM

Clinical Features

- initial changes include microalbuminuria, increased GFR (up to 140%), enlarged kidneys
- microalbuminuria: ACR of >2.0 mg/mmol (men) or >2.8 mg/mmol (women)
- macroalbuminuria: ACR of >20.0 mg/mmol (men) or >28.0 mg/mmol (women)
- progression over 15 years to cause hypertension, persistent proteinuria (macroalbuminuria), nephrotic syndrome, and renal failure
- elevated HbA1C is an independent risk factor for progression to microalbuminuria

Treatment and Prevention

- tight glycemic control
- tight blood pressure control ($<130/80$ mmHg) with ACEI or ARB
- numerous studies have shown that even in the absence of glycemic control, ACEIs or ARBs reduce the level of albuminuria and reduce the rate of progression of renal disease in normotensive and hypertensive patients with Type 1 or Type 2 DM
- Type 1 DM \rightarrow if normotensive or hypertensive and patient has microalbuminuria or macroalbuminuria \rightarrow ACE inhibitors 1st line; ARBs 2nd line
- Type 2 DM \rightarrow if normotensive or hypertensive and patient has microalbuminuria or macroalbuminuria \rightarrow ACE inhibitors or ARBs if creatinine clearance (CrCl) >60 ml/min; ARB if CrCl ≤ 60 ml/min
- consider use of non-dihydropyridine calcium channel blocker (e.g. diltiazem) in those unable to tolerate both ACE inhibitors and ARBs
- limit use of nephrotoxic drugs and dyes
- protein restriction (controversial)
- renal failure may necessitate hemodialysis and renal transplant

Management of Diabetic Retinopathy: A**Systematic Review**

JAMA 2007; 298:902-16

Purpose: To review the best evidence for primary and secondary interventions in the management of diabetic retinopathy (DR), including diabetic macular edema.

Study Selection: All English-language randomized controlled trials (RCTs) with more than 12 months of follow-up and meta-analyses were included. Delphi consensus criteria were used to identify well-conducted studies.

Results: Forty-four studies (including 3 meta-analyses) met the inclusion criteria. Tight glycemic and blood pressure control reduces the incidence and progression of DR. Pan-retinal laser photocoagulation reduces the risk of moderate and severe visual loss by 50% in patients with severe nonproliferative and proliferative retinopathy. Focal laser photocoagulation reduces the risk of moderate visual loss by 50 to 70% in eyes with macular edema. Early vitrectomy improves visual recovery in patients with proliferative retinopathy and severe vitreous hemorrhage. Intravitreal injections of steroids may be considered in eyes with persistent loss of vision when conventional treatment has failed. There is insufficient evidence for the efficacy or safety of lipid-lowering therapy, medical interventions, or antivascular endothelial growth factors on the incidence or progression of DR.

Conclusions: Tight glycemic and blood pressure control remains the cornerstone in the primary prevention of DR. Pan-retinal and focal retinal laser photocoagulation reduces the risk of visual loss in patients with severe DR and macular edema, respectively. There is currently insufficient evidence to recommend routine use of other treatments.

Effects of Treatments for Symptoms of Painful Diabetic Neuropathy: Systematic Review
BMJ 2007; 335:87

Purpose: To evaluate the effects of treatments for the symptoms of painful diabetic neuropathy.

Study Selection: Randomised controlled trials comparing topically applied and orally administered drugs with a placebo in adults with painful diabetic neuropathy.

Results: 25 included reports compared anticonvulsants (n=1270), antidepressants (94), opioids (329), ion channel blockers (173), N-methyl-D-aspartate antagonist (14), duloxetine (805), capsaicin (277), and isosorbide dinitrate spray (22) with placebo. The odds ratios in terms of 50% pain relief were 5.33 (95% confidence interval 1.77 to 16.02) for traditional anticonvulsants, 3.25 (2.27 to 4.66) for newer generation anticonvulsants, and 22.24 (5.83 to 84.75) for tricyclic antidepressants. The odds ratios in terms of withdrawals related to adverse events were 1.51 (0.33 to 6.96) for traditional anticonvulsants, 2.98 (1.75 to 5.07) for newer generation anticonvulsants, and 2.32 (0.59 to 9.69) for tricyclic antidepressants. Insufficient dichotomous data were available to calculate the odds ratios for ion channel blockers.

Conclusion: Anticonvulsants and antidepressants are still the most commonly used options to manage diabetic neuropathy. Oral tricyclic antidepressants and traditional anticonvulsants are better for short term pain relief than newer generation anticonvulsants. Evidence of the long term effects of oral antidepressants and anticonvulsants is still lacking. Further studies are needed on opioids, N-methyl-D-aspartate antagonists, and ion channel blockers.

DIABETIC NEUROPATHY (see *Neurology*, N30)

Epidemiology

- approximately 50% of patients within 10 years of onset of Type 1 DM and Type 2 DM

Pathophysiology

- mechanism poorly understood
- acute cranial nerve palsies and diabetic amyotrophy are thought to be due to ischemic infarction of involved peripheral nerve
- the more common motor and sensory neuropathies are thought to be related to metabolic or osmotic toxicity secondary to increased sorbitol and/or decreased myoinositol (possible mechanisms include accumulation of advanced glycation endproducts (AGE), oxidative stress, protein kinase C, nerve growth factor deficiency)
- can have peripheral sensory neuropathy, motor neuropathy, or autonomic neuropathy

Screening

- 128 Hz tuning fork or 10 g monofilament at diagnosis and annually in people with Type 2 DM and after 5 years duration of Type 1 DM

Clinical Features

Table 13. Clinical Presentation of Diabetic Neuropathies

Peripheral Sensory Neuropathy	Motor Neuropathy	Autonomic Neuropathy
Paresthesias (tingling, itching), neuropathic pain, radicular pain, numbness, decreased tactile sensation	Less common than sensory neuropathy	Postural hypotension, tachycardia, decreased cardiovascular response to Valsalva maneuver
Bilateral and symmetric with decreased perception of vibration and pain/temperature; especially true in the lower extremities but may also be present in the hands	Delayed motor nerve conduction and muscle weakness/atrophy	Gastroparesis and alternating diarrhea and constipation
Decreased ankle reflex	May involve one nerve trunk (mononeuropathy) or more (mononeuritis multiplex)	Urinary retention and erectile dysfunction
Symptoms may first occur in entrapment syndromes e.g. carpal tunnel, neuropathic ulceration of foot	Some of the motor neuropathies spontaneously resolve after 6-8 wks	
	Reversible CN palsies: III (ptosis/ophthalmoplegia), VI (inability to laterally deviate eye), and VII (Bell's palsy)	
	Diabetic amyotrophy: refers to pain, weakness, and wasting of hip flexors or extensors	

Treatment and Management

- tight glycemic control
- for neuropathic pain syndromes: tricyclic antidepressants (e.g. amitriptyline), pregabalin, anti-epileptics (e.g. carbamazepine, gabapentin), and capsaicin
- foot care education
- Jobst® fitted stocking and tilting of head of bed may decrease symptoms of orthostatic hypotension
- treat gastroparesis with domperidone and/or metoclopramide (dopamine antagonists), erythromycin (stimulates motilin receptors)
- medical, mechanical and surgical treatment for erectile dysfunction (see *Urology*, U31)



Other Complications

Dermatologic

- diabetic dermopathy: atrophic brown spots commonly in pretibial region known as "shin spots", secondary to increased glycosylation of tissue proteins or vasculopathy
- eruptive xanthomas secondary to increased triglycerides
- necrobiosis lipidica diabetorum: rare complication characterized by thinning skin over the shins allowing visualization of subcutaneous vessels

Bone and Joint Disease

- juvenile cheiroarthropathy: chronic stiffness of hand caused by contracture of skin over joints secondary to glycosylated collagen and other connective tissue proteins
- Dupuytren's contracture
- bone demineralization: bone density 10-20% below normal
- frozen shoulder

Cataracts

- subcapsular and senile cataracts secondary to glycosylated lens protein or increased sorbitol causing osmotic change and fibrosis

Infections

- see *Infectious Diseases*, ID23

Hypoglycemia

Etiology and Pathophysiology

- hypoglycemia occurs most frequently in people with diabetes receiving insulin or certain antihyperglycemic therapies (insulin secretagogues)
- in people without diabetes, care must be taken to distinguish fasting from post-prandial hypoglycemia as each invokes separate differential diagnoses

Table 14. Common Causes of Hypoglycemia

Fasting		Post-Prandial (Nonfasting, Reactive)
Hyperinsulinism	Without Hyperinsulinism	
<ul style="list-style-type: none"> Exogenous insulin Sulfonylurea reaction Autoimmune hypoglycemia (autoantibodies to insulin or insulin receptor) Pentamidine Pancreatic beta cell tumour – insulinoma 	<ul style="list-style-type: none"> Severe hepatic dysfunction Chronic renal insufficiency Hypocortisolism Alcohol use Non-pancreatic tumours Inborn error of carbohydrate metabolism, glycogen storage disease, gluconeogenic enzyme deficiency 	<ul style="list-style-type: none"> Alimentary Functional Noninsulinoma pancreatogenous hypoglycemic syndrome Occult diabetes Leucine sensitivity Hereditary fructose intolerance Galactosemia Newborn infant of diabetic mother

Clinical Features

- Whipple's triad
 - serum glucose <2.5 mmol/L (45 mg/dL) in males and <2.2 mmol/L (40 mg/dL) in females
 - neuroglycopenic symptoms or adrenergic symptoms (autonomic response)
 - relief provided by administration of glucose
- adrenergic symptoms (typically occur first; caused by autonomic nervous system activity)
 - palpitations, sweating, anxiety, tremor, tachycardia
- neuroglycopenic symptoms (caused by decreased activity of CNS)
 - dizziness, headache, clouding of vision, mental dullness, fatigue, confusion, seizures, coma

Investigations

- electrolytes, BUN/creatinine, LFTs, drugs/toxins

Treatment

- for fasting hypoglycemia, must treat underlying cause
- for post-prandial (reactive) hypoglycemia, frequent small feeds
- see Emergency Medicine, ER36
- bloodwork to be drawn when patient is hypoglycemic (i.e. during hospitalized 72-hour fast): serum ketones, insulin, proinsulin, C-peptide, cortisol, and GH
- treatment of hypoglycemic episode in the unconscious patient or patient NPO
 - D50W 50 mL (1 ampule) IV or 1 mg glucagon SC (if no IV available)
 - may need ongoing glucose infusion once BG >5 mmol/L (90 mg/dL)

Metabolic Syndrome

- defined by having three or more risk factors (see sidebar)
- postulated syndrome related to insulin resistance associated with hyperglycemia, hyperinsulinemia, hypertension, central obesity, and dyslipidemia
- obesity aggravates extent of insulin resistance
- complications include atherosclerosis, CAD, MI, and stroke
- not to be confused with syndrome X related to angina pectoris with normal coronary arteries (Prinzmetal angina)

Obesity

- see Family Medicine, FM5



C-Peptide

A short peptide released into the circulation when proinsulin is cleaved to insulin.



Use C-peptide Levels to Distinguish between Exogenous and Endogenous Source of Hyperinsulinemia

Increased = endogenous
Decreased or normal = exogenous



Treatment of Acute Hypoglycemic Episode (Blood Glucose <4.0 mmol/L) in the Awake Patient (e.g. able to self-treat)

- 1) Eat 15 g of carbohydrates (CHO) (e.g. 3 x 5 g glucose tablets; 3 packets sugar dissolved in water; 3/4 cup of juice)
- 2) Wait 15 minutes
- 3) Retest Blood Glucose (BG)
- 4) Repeat steps 1-3 until BG >5 mmol/L
- 5) Eat next scheduled meal. If next meal is >1 hour away, eat snack including 15 g of CHO and protein.



Hypoglycemia Unawareness: (Type 1 DM >>> Type 2 DM)

Patient remains asymptomatic until severely hypoglycemic levels are reached

Causes:

- Decreased glucagon/epinephrine response
- History of repeated hypoglycemia or low HbA1C
- Autonomic dysfunction



Features of Metabolic Syndrome (International Diabetes Federation, 2005)

Risk Factor	Defining level
Abdominal Obesity	
Men	Waist circumference ≥94 cm (37 inches)
Women	Waist circumference ≥80 cm (31.5 inches)
Triglyceride Level	≥1.7 mmol/L (150 mg/dL)
HDL-C Level	
Men	<1.0 mmol/L (<40 mg/dL)
Women	<1.3 mmol/L (<50 mg/dL)
Blood Pressure	≥130/80 mmHg
Fasting Glucose Level	≥5.6 mmol/L (>100 mg/dL)

Pituitary Gland

Pituitary Hormones



The Pituitary Hormones

"Go Look For The Adenoma Please"
GH, LH, FSH, TSH, ACTH, PRL +
posterior pituitary hormones: ADH and
oxytocin

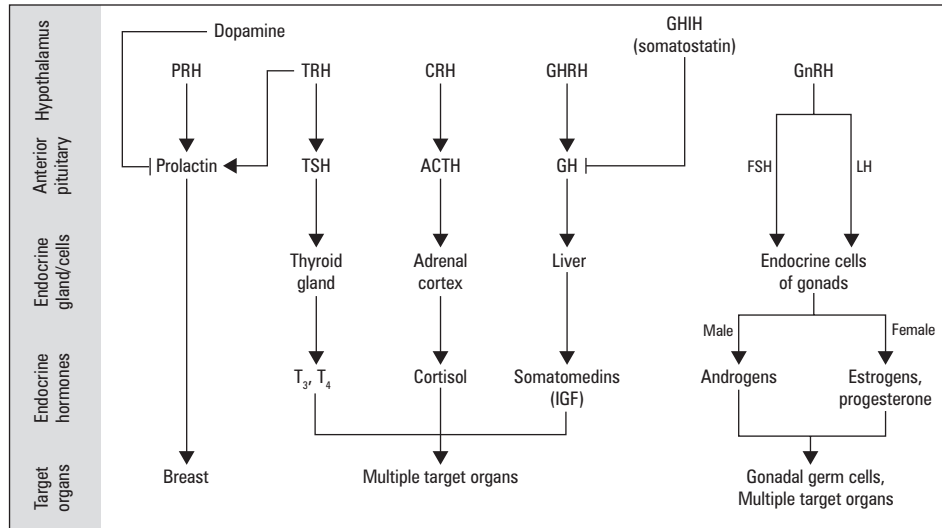


Figure 7. Hypothalamo-Pituitary Hormonal Axes

CRH = corticotrophin-releasing hormone; GnRH = gonadotropin-releasing hormone; GHIH = growth hormone-inhibiting hormone; GHRH = growth hormone-releasing hormone; PRH = prolactin-releasing hormone; TRH = thyrotropin-releasing hormone

Hypothalamic Control of Pituitary

- trophic and inhibitory factors control the release of pituitary hormones
- most hormones are primarily under trophic stimulation except prolactin which is primarily under inhibitory control by dopamine
- transection of the pituitary stalk (i.e. dissociation of hypothalamus and pituitary) leads to pituitary hypersecretion of prolactin and hyposcretion of all remaining hormones

Anterior Pituitary Hormones

- growth hormone (GH), luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), and prolactin (PRL)

Posterior Pituitary (Hypothalamic) Hormones

- antidiuretic hormone (ADH) and oxytocin
- peptides synthesized in the supraoptic and paraventricular nuclei of the hypothalamus
- although ADH and oxytocin are produced in the hypothalamus, these hormones are stored and released from the posterior pituitary

Table 15. The Physiology and Action of Pituitary Hormones

Hormone	Function	Physiology	Inhibitory Stimulus	Secretory Stimulus
ACTH	<ul style="list-style-type: none"> • Stimulates growth of adrenal cortex and secretion of its hormones 	<ul style="list-style-type: none"> • Polypeptide • Pulsatile and diurnal variation (peaks at 02:00-04:00; lowest at 18:00-24:00) 	<ul style="list-style-type: none"> • Dexamethasone • Cortisol 	<ul style="list-style-type: none"> • CRH • Metyrapone • Insulin-induced hypoglycemia • Fever, pain, stress
ADH	<ul style="list-style-type: none"> • Acts at renal collecting ducts to cause insertion of aquaporin channels and increases water reabsorption thereby concentrating urine 	<ul style="list-style-type: none"> • Octapeptide • Osmoreceptors in hypothalamus detect serum osmolality • Contracted plasma volume detected by baroreceptors is a more potent stimulus than osmolality 	<ul style="list-style-type: none"> • ↓ serum osmolality 	<ul style="list-style-type: none"> • Hypovolemia or ↓ effective circulatory volume • ↑ serum osmolality • Stress, pain, fever, paraneoplastic • Lung or brain pathology
GH	<ul style="list-style-type: none"> • Needed for linear growth • IGF stimulates growth of bone and cartilage 	<ul style="list-style-type: none"> • Polypeptide • Acts indirectly through serum factors synthesized in the liver: IGF (somatomedins) • Serum GH undetectable for most of the day and suppressed after meals high in glucose • Sustained rise during sleep 	<ul style="list-style-type: none"> • Glucose challenge • Glucocorticoids • Hypothyroidism • Somatostatin • Dopamine agonists • IGF-1 (long-loop) • Tonically by dopamine • D₂ receptor agonists 	<ul style="list-style-type: none"> • Insulin-induced hypoglycemia • Exercise • REM sleep • Arginine, clonidine, propranolol, L-dopa • GHRH

Table 15. The Physiology and Action of Pituitary Hormones (continued)

Hormone	Function	Physiology	Inhibitory Stimulus	Secretory Stimulus
LH/FSH	<ul style="list-style-type: none"> Stimulate gonads via cAMP Ovary: <ul style="list-style-type: none"> LH: production of androgens (thecal cells) which are converted to estrogens (granulosa cells); induces luteinization in follicles FSH: growth of granulosa cells in ovarian follicle; controls estrogen formation Testes: <ul style="list-style-type: none"> LH: production of testosterone (Leydig cells) FSH: production of spermatozoa (Sertoli cells) 	<ul style="list-style-type: none"> Polypeptide Glycoproteins (similar alpha subunit TSH and hCG) Secreted in pulsatile fashion 	<ul style="list-style-type: none"> Estrogen Progesterone Testosterone Inhibin Continuous (i.e. non-pulsatile) GnRH infusion 	<ul style="list-style-type: none"> Pulsatile GnRH
Oxytocin	<ul style="list-style-type: none"> Causes uterine contraction Breast milk secretion 	<ul style="list-style-type: none"> Nonapeptide 	<ul style="list-style-type: none"> EtOH 	<ul style="list-style-type: none"> Suckling Distention of female genital tract via stretch receptors
Prolactin	<ul style="list-style-type: none"> Promotes milk production Inhibits GnRH secretion 	<ul style="list-style-type: none"> Polypeptide Episodic secretion 		<ul style="list-style-type: none"> Sleep Stress, hypoglycemia Pregnancy, breast-feeding Mid-menstrual cycle Sexual activity TRH Drugs: psychotropics, antihypertensives, dopamine antagonists, opiates, high dose estrogen
TSH	<ul style="list-style-type: none"> Stimulates growth of thyroid and secretion of T_3 and T_4 via cAMP 	<ul style="list-style-type: none"> Glycoprotein 	<ul style="list-style-type: none"> Circulating thyroid hormones (T_3, T_4) Opiates, dopamine 	<ul style="list-style-type: none"> TRH Epinephrine Prostaglandins

Growth Hormone (GH)



GH DEFICIENCY

- cause of short stature in children (see [Pediatrics](#), P35)
- controversial significance in adults

GH EXCESS

- gigantism
 - excess GH secretion before epiphyseal fusion
- acromegaly
 - excess GH secretion in adults (after epiphyseal fusion)

Etiology

- GH secreting pituitary adenoma, carcinoid or pancreatic islet tumours secreting ectopic GHRH resulting in excess GH

Pathophysiology

- normally, growth hormone is a catabolic hormone that acts to increase blood glucose levels
- in growth hormone excess states, secretion remains pulsatile, but there is loss of hypoglycemic stimulation, glucose suppression and the nocturnal surge
- proliferation of bone, cartilage, soft tissues, organomegaly
- insulin resistance and IGT

Clinical Features

- enlargement of hands and feet, coarsening of facial features, thickening of calvarium, prognathism, thickening of skin, increased sebum production, sweating, acne, sebaceous cysts, fibromata mollusca, acanthosis nigricans, arthralgia, degenerative osteoarthritis (OA), thyromegaly, renal calculi, hypertension, cardiomyopathy, and DM

Investigations

- glucose suppression test (OGTT) is the most specific test → increased GH in acromegaly
- insulin-like growth factor-1 (IGF-1)

Treatment

- surgery, octreotide (somatostatin analogue), growth hormone receptor antagonist, bromocriptine (dopamine agonist, acts on the pituitary gland to block the production and release of growth hormone), radiation



Signs and Symptoms of Acromegaly:

ABCDEF

Arthralgia/Arthritis
Blood pressure raised
Carpal tunnel syndrome
Diabetes
Enlarged organs
Field defect (visual)

**Approach to Nipple Discharge**

1. Differentiate between galactorrhea (fat droplets present) versus breast discharge (usually unilateral, may be bloody or serous)
2. If galactorrhea, determine if physiologic (e.g. pregnancy, lactation, stress) versus pathologic
3. If abnormal breast discharge, must rule out a breast malignancy

Prolactin (PRL)

HYPERPROLACTINEMIA

Etiology

- prolactinoma: most common pituitary adenoma (prolactin-secreting tumours may be induced by estrogens and grow during pregnancy)
- pituitary stalk lesions
- primary hypothyroidism (increased TRH)
- chronic renal failure resulting in decreased clearance, biliary cirrhosis
- medications with anti-dopaminergic properties are a common cause of high prolactin levels: antipsychotics, antidepressants, antihypertensives, anti-migraine agents (triptans/ergotamines), bowel motility agents (metoclopramide), H₂-blockers (e.g. ranitidine)

Clinical Features

- galactorrhea (secretion of breast milk in men or non-lactating women), infertility, hypogonadism, amenorrhea

Investigations

- serum PRL, TSH, liver enzyme tests, creatinine
- MRI

Treatment

- long-acting dopamine agonist: bromocriptine, cabergoline or quinagolide (Norprolac®)
- surgery ± radiation (rare)
- prolactin-secreting tumours are very slow-growing and sometimes require no treatment
- if medication-induced, consider stopping medication if possible

Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH)

HYPOGONADOTROPISM

Clinical Features

- hypogonadism, amenorrhea, erectile dysfunction (ED), loss of body hair, fine skin, testicular atrophy, failure of pubertal development

Treatment

- Pergonal® (combined FSH/LH hormone therapy), hCG, or GnRH analogue if fertility desired
- symptomatic treatment with estrogen/testosterone

HYPERGONADOTROPISM

- 2° hypersecretion in gonadal failure

Antidiuretic Hormone (ADH)

DIABETES INSIPIDUS (DI)

Definition

- disorder resulting from deficient ADH action causing passage of large volumes of dilute urine

Diagnostic Criteria

- fluid deprivation will differentiate true DI (high urine output persists, urine osmolality < plasma osmolality) from psychogenic DI (psychogenic polydipsia)
- response to exogenous ADH will distinguish central from nephrogenic DI

Etiology and Pathophysiology

- central DI: insufficient ADH due to post-pituitary surgery, tumours, stalk lesion, hydrocephalus, histiocytosis, trauma, familial central DI
- nephrogenic DI: collecting tubules in kidneys resistant to ADH (drugs including lithium, hypercalcemia, hypokalemia, chronic renal disease, hereditary nephrogenic DI)
- psychogenic polydipsia must be ruled out

Clinical Features

- passage of large volumes of dilute urine, polydipsia, dehydration

Treatment

- DDAVP/vasopressin for total DI
- DDAVP, chlorpropamide, clofibrate, or carbamazepine for partial DI
- nephrogenic DI treated with solute restriction and thiazide diuretics

**Diagnosing Subtypes of DI with DDAVP Response**

Concentrated urine = Central
No effect = Nephrogenic

SYNDROME OF INAPPROPRIATE ADH SECRETION (SIADH)

Diagnostic Criteria

- hyponatremia with corresponding plasma hypo-osmolality, urine sodium concentration above 40 mEq/L, urine less than maximally diluted (>100 mOsm/kg), euvolemia (edema absent), and absence of adrenal, renal or thyroid insufficiency

Etiology and Pathophysiology

- stress (pain, nausea, post-surgical)
- malignancy (lung, pancreas, lymphoma)
- CNS disease (inflammatory, hemorrhage, tumour, Guillain-Barré syndrome)
- respiratory disease (TB, pneumonia, empyema)
- drugs (vincristine, chlorpropamide, cyclophosphamide, carbamazepine, nicotine, morphine, DDAVP, oxytocin)

Treatment

- treat underlying cause, fluid restriction, vasopressin receptor antagonists (e.g. tolvaptan, conivaptan), and demeclocycline (antibiotic with anti-ADH properties, rarely-used)



SIADH vs. Cerebral Salt Wasting (CSW)
CSW can occur in cases of subarachnoid hemorrhage. Na is excreted by malfunctioning renal tubules, mimicking findings of SIADH.

Pituitary Pathology

PITUITARY ADENOMA (see Neurosurgery, NS13)

Clinical Features

- related to size and location
 - visual field defects (usually bitemporal hemianopsia), oculomotor palsies, increased ICP
 - skull radiograph (rarely done): "double floor" (large sella or erosion), calcification
 - CT and MRI far more sensitive for diagnosis
- related to destruction of gland
 - hypopituitarism
- related to increased hormone secretion
 - PRL (galactorrhea), GH (acromegaly in adults, gigantism in children), ACTH (Cushing's disease = Cushing's syndrome caused by a pituitary tumour)
 - tumours secreting LH, FSH and TSH are rare

EMPTY SELLA SYNDROME

- occurs when subarachnoid space extends into sella turcica, partially filling it with CSF resulting in remodeling and enlargement of sella turcica and flattening of the pituitary gland
- usually eupituitary
- may have headaches
- MRI may show herniation of diaphragm sellae and the presence of CSF in the sella turcica
- no treatment necessary

PITUITARY APOPLEXY

- acute hemorrhage/infarction of pituitary tumour
- sudden severe headache, altered level of consciousness
- ocular symptoms: ophthalmoplegia with pituitary tumour likely indicates apoplexy since tumour rarely gets big enough to encroach on cranial nerves
- neurosurgical emergency: acute decompression of pituitary via trans-sphenoidal route

HYPOPITUITARISM

Etiology

- the eight "I"s
 - Invasive: generally primary tumours
 - Infarction: e.g. Sheehan's syndrome (excessive post-partum blood loss leading to infarction of the pituitary gland)
 - Infiltrative disease: e.g. sarcoidosis, hemochromatosis, histiocytosis
 - Iatrogenic: following surgery or radiation
 - Infectious: e.g. syphilis, TB
 - Injury: severe head trauma
 - Immunologic: autoimmune destruction
 - Idiopathic: familial forms, congenital midline defects

Clinical Features

- typical clinical progression in panhypopituitarism
 - GH (most common deficiency) \rightarrow LH/FSH \rightarrow ACTH \rightarrow TSH
- fall in GH is not clinically apparent
- fall in PRL is variable, but may present as decreased lactation
- gonadotropin insufficiency causes erectile dysfunction in men and amenorrhea or infertility in women
- TSH deficiency produces clinical hypothyroidism
- ACTH deficiency leads to adrenal insufficiency



Important deficiencies to recognize are:
1. Adrenal insufficiency
2. Hypothyroidism

Concurrent adrenal insufficiency and hypothyroidism should be treated with glucocorticoids first and then with thyroid hormone to avoid adrenal crisis.

Regulation of Thyroid Function

- extrathyroid
 - stimulation of thyroid by TSH, epinephrine, prostaglandins (cAMP stimulators)
 - T₃ negatively feeds back on anterior pituitary to inhibit TSH and on hypothalamus to inhibit TRH
- intrathyroid (autoregulation)
 - increasing iodide supply inhibits iodide organification, thus decreasing T₃ and T₄ synthesis (Wolff-Chaikoff effect)
 - there is varying thyroid sensitivity to TSH in response to iodide availability
 - increased ratio of T₃ to T₄ in iodide deficiency
 - increased activity of peripheral 5' deiodinase in hypothyroidism increases T₃ production despite low T₄ levels

Table 16. Summary of Treatments for Hyperthyroidism and Hypothyroidism

Hyperthyroidism	Hypothyroidism
Propylthiouracil	L-thyroxine (dosing different if elderly)
Methimazole	Liothyronine (T ₃)
Beta-blockers	
Ablation with Radioactive Iodine	
Surgical Resection	

Tests of Thyroid Function and Structure

TSH

- sensitive TSH (sTSH) is the best test for assessing thyroid function
- hyperthyroidism
 - primary: TSH is low because of negative feedback from increased levels of circulating T₃ and T₄
 - secondary: increased TSH which results in increased T₃ and T₄
- hypothyroidism
 - primary: increased TSH (most sensitive test) because of less negative feedback from T₃ and T₄
 - secondary: TSH is low with variable response to TRH depending on the site of the lesion (pituitary or hypothalamic)

Free T₃ and Free T₄

- total T₃ and T₄ levels depend on amount of TBG
- TBG increases with pregnancy, oral contraceptive (OCP) use, acute infectious hepatitis, biliary cirrhosis
- TBG decreases with androgens, glucocorticoids, cirrhosis, hyponatremia, phenytoin, ASA, NSAIDs, nephrotic syndrome, severe systemic illness
- free T₃ and T₄ are independent of TBG and measure biological activity
- standard assessment of thyroid function measures TSH and if necessary free T₄ and free T₃

Thyroid Autoantibodies

- thyroglobulin antibodies (TgAb), thyroid peroxidase (microsomal antibodies), TSH receptor inhibiting antibodies
 - increased in Hashimoto's disease; normal variant in 10-20% of individuals
- thyroid stimulating immunoglobulin (TSI)
 - increased in Graves' disease

Plasma Thyroglobulin

- used to monitor residual thyroid activity post-thyroidectomy, e.g. for thyroid cancer recurrence
- undetectable levels may suggest cure, especially on hormone suppression
- normal or elevated levels may suggest persistent, recurrent, or metastatic disease, especially on stimulation

Serum Calcitonin

- not routinely done to investigate thyroid nodules
- ordered if suspicion of medullary thyroid carcinoma or family history of MEN IIa or IIb syndromes

Thyroid Imaging/Scans

- normal gland size 15-20 g (estimated by palpation)
- thyroid U/S
 - to measure size of gland, solid vs. cystic nodule, facilitate FNAB
- thyroid scan (Technetium-99)
 - differentiates between hot (functioning) and cold (non-functioning) nodules
 - to distinguish between three major types of high-uptake hyperthyroidism
 - Graves' disease (diffuse uptake)
 - toxic multinodular goitre (multiple discrete areas)
 - solid toxic adenoma (single intense area of uptake)
 - test of structure – order if there is a thyroid nodule and patient is hyperthyroid



Thyroid Assessment

- Serum thyroid hormones (TSH, T₃, T₄)
- Antibodies
- Thyroglobulin
- Thyroid imaging/scans
- Biopsy (FNA)

Does this Patient have a Goitre?

JAMA 1995; 273:813-17

Clinical diagnosis was based on degree of lateral prominence, visibility, and palpability of the thyroid gland. Most primary studies did not report the specifics of thyroid examination technique, and therefore no evidence exists to support the superiority of any one method.

The combined results of 9 studies detail the accuracy of the clinical examination for the presence of goitre (using ultrasound or autopsy as the gold standard for comparison):

Sensitivity	70% (68%-73%)
Specificity	82% (79%-85%)
LR+	3.8 (3.3 to 4.5)
LR-	0.37 (0.33 to 0.40)

The combined results of 4 studies detail the predictive utility of assessing grades of thyroid gland weight:

Weight	Reference	LR+	95% CI
0-20 g	normal	0.15	(0.10-0.21)
20-40 g	1-2x	1.9	(1.1-3.0)
>40 g	>2x	25.0	(2.6-175)

- radioactive iodine uptake (RAIU)
 - RAIU measures the turnover of iodine by thyroid gland in vivo
 - in areas of low iodine intake and endemic goitre, 24 h RAIU may be as high as 60-90%
 - in areas of high iodine intake, normal 24 h RAIU will be 8-30%
 - RAIU is high in Graves' disease or toxic nodular goitre and low in subacute thyroiditis, active phase of Hashimoto's thyroiditis, and excess iodine intake (e.g. amiodarone, which has high iodine content)
 - test of function – order if patient is hyperthyroid

Thyroid Biopsy

- fine needle aspiration (FNA) for cytology
 - differentiates between benign and malignant disease

Table 17. Summary of Diagnostic Testing in Hyperthyroidism and Hypothyroidism

	Hyperthyroidism	Hypothyroidism
TSH	<ul style="list-style-type: none"> Decreased in primary hyperthyroidism Increased in secondary hyperthyroidism 	<ul style="list-style-type: none"> Increased in primary hypothyroidism Decreased in secondary hypothyroidism
Free T₄	<ul style="list-style-type: none"> Increased in primary hyperthyroidism Increased in secondary hyperthyroidism 	<ul style="list-style-type: none"> Decreased in primary hypothyroidism Decreased in secondary hypothyroidism
RAIU	Graves – increased; homogenous Multinodular Goitre – increased; heterogenous Toxic Nodule – increased in a specific area with suppression elsewhere	No uptake – subacute thyroiditis, antithyroid drugs, recent iodine load
Antibodies	Graves – Thyroid stimulating Ig (TSI)	Hashimoto's – Antithyroid peroxidase (TPO)

Common Etiologies

Table 18. Common Etiologies

Thyrotoxicosis	Hypothyroidism
Graves' Disease	Hashimoto's
Toxic Nodular Goitre	Congenital
Toxic Nodule	Iatrogenic
Thyroiditis	Hypothyroid phase of thyroiditis

Thyrotoxicosis

Definition

- clinical, physiological, and biochemical findings in response to elevated thyroid hormone

Epidemiology

- 1% of general population (4-5% of elderly women)
- F:M = 5:1

Etiology and Pathophysiology

Table 19. Differential Diagnosis of Thyrotoxicosis

Disorder	TSH	Free T ₄ /T ₃	Thyroid Antibodies	RAIU	Other
Hyperthyroidism					
Graves' disease	Decreased	Increased	TSI	Increased	
Toxic Nodular Goitre	Decreased	Increased	—	Increased	
Toxic Nodule	Decreased	Increased	—	Increased	
Thyroiditis	Decreased	Increased	Up to 50% of cases	Decreased	In classical subacute thyroiditis, ESR increased
McCune-Albright syndrome	Decreased	Increased	—	—	At least 2 of polyostotic fibrous dysplasia, café au lait spots, and autonomous endocrine hyperfunction
Jod Basedow	Decreased	Increased	—	Decreased	Iodine induced
Extrathyroidal Sources of Thyroid Hormone					
<ul style="list-style-type: none"> Endogenous (struma ovariae, ovarian teratoma, metastatic follicular carcinoma) 	Decreased	Increased	—	Decreased	
<ul style="list-style-type: none"> Exogenous (drugs) 					

Table 19. Differential Diagnosis of Thyrotoxicosis (continued)

Disorder	TSH	Free T ₄ /T ₃	Thyroid Antibodies	RAIU	Other
Excessive Thyroid Stimulation					
• Pituitary thyrotrophoma	Increased	Increased	—	Increased	
• Pituitary thyroid hormone receptor resistance	Increased	Increased	—	Increased	
• Increased hCG (e.g. pregnancy)	Decreased	Increased	—	Increased	

Clinical Features**Table 20. Clinical Features of Thyrotoxicosis**

General	Fatigue, heat intolerance, irritability, fine tremor
Cardiovascular	Tachycardia, atrial fibrillation, palpitations Elderly patients may have only cardiovascular symptoms, commonly new onset atrial fibrillation
GI	Weight loss with increased appetite, thirst, increased frequency of bowel movements (hyperdefecation)
Neurology	Proximal muscle weakness, hypokalemic periodic paralysis (common in Asians)
GU	Oligomenorrhea, amenorrhea, decreased fertility
Dermatology	Fine hair, skin moist and warm, vitiligo, soft nails with onycholysis (Plummer's nails), clubbing (acropachy), palmar erythema, pretibial myxedema
MSK	Decreased bone mass, proximal muscle weakness
Hematology	Leukopenia, lymphocytosis, splenomegaly, lymphadenopathy (occasionally in Graves' disease)

Treatment

- antithyroid drugs (thionamides: propylthiouracil (PTU) or methimazole (MMI)) for Graves' disease
- beta-blockers for symptom control
- radioactive iodine thyroid ablation
- surgery

Graves' Disease**Definition**

- syndrome characterized by hyperthyroidism with any one of the following features including diffuse goitre, ophthalmopathy, dermopathy (need not appear together)

Epidemiology

- most common cause of thyrotoxicosis
- occurs at any age with peak in 3rd and 4th decade
- F > M = 7:1, 1.5-2% of U.S. women
- familial predisposition: 15% of patients have a close family member with Graves' disease and 50% have family members with positive circulating antibodies
- association with HLA B8 and DR3
- may be associated with other inherited autoimmune disorders (e.g. pernicious anemia, Hashimoto's disease)

Etiology and Pathophysiology

- autoimmune disorder due to a defect in T-suppressor cells
- B lymphocytes produce TSI that binds the TSH receptor and stimulates the thyroid gland
- immune response can be triggered by pregnancy (especially postpartum), iodine excess, lithium therapy, viral or bacterial infections, glucocorticoid withdrawal
- cause of ophthalmopathy uncertain (can occur even when euthyroid) but may include:
 - antibodies against extraocular muscle antigens (fibroblasts implicated) with lymphocytic infiltration
 - glycosaminoglycan deposition
- dermopathy may be related to cutaneous glycosaminoglycan deposition

Clinical Features

- diffuse thyroid goitre ± thyroid bruit secondary to increased blood flow through the gland
- ophthalmopathy: proptosis, lid lag, lid retraction, diplopia, characteristic stare, conjunctival injection
- dermopathy (rare): pretibial myxedema (thickening of dermis that manifests as *non-pitting* edema)
- acropachy: clubbing and thickening of distal phalanges

Investigations

- low TSH
- increased free T₄ (and/or increased T₃)
- positive for TSI



Signs and Symptoms of hyperTHYROIDISM

- Tremor
- Heart rate up
- Yawning (fatigued)
- Restlessness
- Oligomenorrhea/amenorrhea
- Intolerance to heat
- Diarrhea
- Irritability
- Sweating
- Muscle wasting/weight loss



Caution with Thionamides

These drugs are effective in controlling hyperthyroidism and induce permanent remission in 20-30% of patients with Graves' disease. They inhibit thyroid hormone synthesis. They may be used long-term, although they are most often employed to help patients achieve a euthyroid state before definitive treatment.

Severe adverse effects have been rarely reported, and thus use of thionamides is controversial. Adverse effects include teratogenicity, agranulocytosis, hepatotoxicity and ANCA-positive vasculitis.



Radioiodine Therapy for Graves' Disease and the Effect on Ophthalmopathy – A Systematic Review

Clin Endocrinol (Oxf) 2008; Apr 21

Purpose: To assess whether radioiodine therapy (RAI) for Graves' disease GD is associated with increased risk of ophthalmopathy compared with antithyroid drugs (ATDs) or surgery. To assess the efficacy of glucocorticoid prophylaxis in the prevention of occurrence or progression of ophthalmopathy, when used with RAI.

Study Selection: Randomized controlled trials regardless of language or publication status.

Results: RAI was associated with an increased risk of ophthalmopathy compared with ATD (Relative Risk (RR) 4.23, 95% confidence interval (CI): 2.04 to 8.77) but compared with thyroidectomy, there was no statistically significant increased risk (RR 1.59, 95% CI 0.89 to 2.81). The risk of severe GO was also increased with RAI compared with ATD (RR 4.35, 95% CI 1.28 to 14.73). Prednisolone prophylaxis for RAI was highly effective in preventing the progression of GO in patients with pre-existing GO (RR 0.03; 95% CI 0.00 to 0.24). The use of adjunctive ATD with RAI was not associated with any significant benefit on the course of GO.

Conclusions: Radioiodine therapy for Graves' disease is associated with a small but definite increased risk of development or worsening of Graves' ophthalmopathy compared with antithyroid drugs. Steroid prophylaxis is beneficial for patients with pre-existing Graves' ophthalmopathy.

Treatment

- thionamides
 - propylthiouracil (PTU) or methimazole (MMI)
 - inhibit thyroid hormone synthesis by inhibiting peroxidase-catalyzed reactions, thereby inhibiting organification of iodide, blocking the coupling of iodotyrosines, and inhibiting peripheral deiodination of T_4 to T_3
 - most useful in young patients with small glands and mild disease
 - continue treatment until remission occurs (20-40% of patients achieve spontaneous remission at 6-18 months of treatment)
 - small goitre and recent onset are good indicators for long-term remission with medical therapy
 - MMI contraindicated in pregnancy (teratogenic)
 - major side effects: hepatitis and agranulocytosis
 - minor side effects: rash, fever and arthralgias
 - iodinated contrast agents: sodium ipodate and iopanoic acid can inhibit conversion of T_4 to T_3 and are especially effective in combination with MMI
- symptomatic treatment with beta-blockers
- thyroid ablation with radioactive ^{131}I if PTU or MMI trial does not produce disease remission
 - high incidence of hypothyroidism after ^{131}I , requiring lifelong thyroid hormone replacement
 - contraindicated in pregnancy
- subtotal thyroidectomy (indicated rarely for large goitres)
 - risks include hypoparathyroidism and vocal cord palsy
- ophthalmopathy
 - prevent drying
 - high dose prednisone in severe cases
 - orbital radiation, surgical decompression

Prognosis

- course involves remission and exacerbation unless gland is destroyed by radioactive iodine or surgery
- lifetime follow-up needed
- risk of relapse is 37%, 21%, 6% in thionamides, radioiodine ablation, and surgery groups, respectively

Subacute Thyroiditis (Thyrotoxic Phase)

Definition

- acute inflammatory disorder of the thyroid gland characterized by an initial thyrotoxic state followed by hypothyroidism, eventually followed by euthyroidism in most cases
- two subtypes: painful and painless

Etiology and Pathophysiology

- acute inflammation of the thyroid gland characterized by giant cells and lymphocytes
- disruption of thyroid follicles by inflammatory process results in the release of stored hormone rather than excessive production of new thyroid hormone
- painful = viral (usually preceded by URTI), De Quervain's (granulomatous thyroiditis)
- painless = postpartum, auto-immune, lymphocytic
 - occurs in 5-10% of postpartum mothers and is symptomatic in 1/3 of patients

Clinical Features

- thyroid gland enlargement
- two forms
 - painful ("De Quervain's") thyroid, ears, jaw and occiput
 - painless ("Silent")
- fever and malaise may be present, especially in De Quervain's
- postpartum: thyrotoxicosis 2-3 months postpartum with a subsequent hypothyroid phase at 4-8 months postpartum
- may be mistakenly diagnosed as postpartum depression

Laboratory Investigations

- elevated free T_4 , T_3 , low TSH, RAIU markedly reduced
- marked elevation of ESR in painful variety only
- as disease progresses, values consistent with hypothyroidism may appear
- rise in RAIU reflects gland recovery

Treatment

- painful – high dose anti-inflammatories (NSAIDs), prednisone may be required for severe pain, fever, or malaise
- iodinated contrast agents (e.g. iopanoic acid, ipodate) to inhibit peripheral conversion of TH to T_3
- beta-adrenergic blockade is usually effective in reversing most of the hypermetabolic and cardiac symptoms in both subtypes
- if symptomatically hypothyroid may treat short-term with thyroxine

Prognosis

- full recovery in most cases, but permanent hypothyroidism in 10% of painless thyroiditis
- postpartum: most resolve spontaneously without need for supplementation, however may recur with subsequent pregnancies

Toxic Adenoma/Toxic Multinodular Goitre

Etiology and Pathophysiology

- autonomous thyroid hormone production from a functioning adenoma that is hypersecreting T_3 and T_4
- may be singular (toxic adenoma) or multiple (toxic multinodular goitre [Plummer's disease])

Clinical Features

- goitre with adenomatous changes
- tachycardia, heart failure, arrhythmia, weight loss, nervousness, weakness, tremor, and sweats
- atrial fibrillation is a common presentation in the elderly
- seen most frequently in elderly people, often with presentation of atrial fibrillation

Investigations

- low TSH, high T_3 and T_4 (with a larger increase in T_3)
- thyroid scan with increased uptake in nodule(s), and suppression of the remainder of the gland

Treatment

- initiate therapy with PTU or MMI to attain euthyroid state in order to avoid radiation thyroiditis, use high dose radioactive iodine to ablate tissue over weeks
- propranolol often necessary for symptomatic treatment prior to definitive therapy
- surgery may also be used as 1st line treatment

Thyrotoxic Crisis/Thyroid Storm

Definition

- acute exacerbation of all of the symptoms of thyrotoxicosis presenting in a life threatening state secondary to uncontrolled hyperthyroidism – this is a MEDICAL EMERGENCY!

Etiology and Pathophysiology

- often precipitated by infection, trauma, or surgery in a hyperthyroid patient

Differential Diagnosis

- sepsis, pheochromocytoma, malignant hyperthermia, drug overdose

Clinical Features

- hyperthyroidism
- extreme fever (hyperthermia), tachycardia, vomiting, diarrhea, vascular collapse, hepatic failure with jaundice, and confusion
- arrhythmia that may lead to congestive heart failure, pulmonary edema
- mental status changes ranging from delirium to coma

Laboratory Investigations

- increased free T_3 , T_4 , undetectable TSH
- \pm anemia, leukocytosis, hypercalcemia, elevated LFTs

Treatment

- principles are the same as in hyperthyroidism except use higher doses and frequencies
- initiate prompt therapy; do not wait for confirmation from lab
- propranolol (IV) for tachycardia and to decrease peripheral conversion of T_4 to T_3 (watch for CHF)
- supportive: fluid and electrolytes, diuresis, vasopressors, cooling blanket, acetaminophen for pyrexia
- high dose PTU
- iodide (NaI, KI, Lugol's solution) to inhibit release of thyroid hormone
- lithium to inhibit release of thyroid hormone
- dexamethasone to block peripheral conversion, to lower body temperature, and to treat possible underlying autoimmune condition
- if extreme, plasmapheresis or dialysis to remove high circulating thyroid hormone
- treat precipitant

Prognosis

- 50% mortality rate

Hypothyroidism

Thyroid Hormone Replacement for Subclinical Hypothyroidism

Cochrane Database Syst Rev 2007; (3):CD003419

Purpose: To assess the effects of thyroid hormone replacement for subclinical hypothyroidism.

Study Selection: Randomised controlled trials comparing thyroid hormone replacement with placebo or no treatment in adults with subclinical hypothyroidism. Minimum duration of follow-up was one month.

Results: No trial assessed (cardiovascular) mortality or morbidity. Seven studies evaluated symptoms, mood and quality of life with no statistically significant improvement. One study showed a statistically significant improvement in cognitive function. Six studies assessed serum lipids, there was a trend for reduction in some parameters following levothyroxine replacement. Some echocardiographic parameters improved after levothyroxine replacement therapy, like myocardial relaxation, as indicated by a significant prolongation of the isovolumic relaxation time as well as diastolic dysfunction. Only four studies reported adverse events with no statistically significant differences between groups.

Conclusions: In current RCTs, levothyroxine replacement therapy for subclinical hypothyroidism did not result in improved survival or decreased cardiovascular morbidity. Data on health-related quality of life and symptoms did not demonstrate significant differences between intervention groups. Some evidence indicates that levothyroxine replacement improves some parameters of lipid profiles and left ventricular function.



Signs and Symptoms of Hypothyroidism

HIS FIRM CAP

Hypoventilation
Intolerance to cold

Slow HR

Fatigue

Impotence

Renal impairment

Menorrhagia/amenorrhea

Constipation

Anemia

Paresthesia

Definition

- clinical syndrome caused by cellular responses to insufficient thyroid hormone production

Epidemiology

- 2-3% of general population
- F:M = 10:1
- 10-20% of women over age 50 have subclinical hypothyroidism (normal T₄, TSH mildly elevated)
- iodine deficiency most common cause worldwide, but not in North America

Etiology and Pathophysiology

- primary hypothyroidism (90%)
 - inadequate thyroid hormone production secondary to intrinsic thyroid defect
 - iatrogenic: post-ablative (¹³¹I or surgical thyroidectomy)
 - autoimmune: Hashimoto's thyroiditis, chronic thyroiditis, idiopathic, burnt out Graves'
 - hypothyroid phase of subacute thyroiditis
 - drugs: goitrogens (iodine), PTU, MMI, lithium
 - infiltrative disease (progressive systemic sclerosis, amyloid)
 - iodine deficiency
 - congenital (1/4000 births)
 - neoplasia
- secondary hypothyroidism: pituitary hypothyroidism
 - insufficiency of pituitary TSH
- tertiary hypothyroidism: hypothalamic hypothyroidism
 - decreased TRH from hypothalamus (rare)
- peripheral tissue resistance to thyroid hormone (Refetoff syndrome)

Table 21. Interpretation of Serum TSH and Free T₄ in Hypothyroidism

	Serum TSH	Free T ₄
Overt Primary Hypothyroidism	Increased	Decreased
Subclinical Primary Hypothyroidism	Increased	Normal
Secondary Hypothyroidism	Decreased or not appropriately elevated	Decreased

Clinical Features

Table 22. Clinical Features of Hypothyroidism

General	Fatigue, cold intolerance, slowing of mental and physical performance, hoarseness, macroglossia
CVS	Slow pulse, pericardial effusion, bradycardia, hypertension, worsening CHF + angina, hypercholesterolemia, hyperhomocysteinemia, myxedema heart
GI	Weight gain despite poor appetite, constipation
Neurology	Paresthesia, slow speech, muscle cramps, delay in relaxation phase of deep tendon reflexes ("hung reflexes"), Carpal Tunnel syndrome, asymptomatic increase in CK, seizures
GU	Menorrhagia, amenorrhea, impotence
Dermatology	Puffiness of face, periorbital edema, cool and pale, dry and rough skin, hair dry and coarse, eyebrows thinned (lateral 1/3), discolouration (carotenemia)
Hematology	Anemia: 10% pernicious due to presence of anti-parietal cell antibodies
Respiratory	Decreased exercise capacity, hypoventilation secondary to weak muscles, decreased pulmonary responses to hypoxia, sleep apnea due to macroglossia

Treatment

- L-thyroxine (dose range: 0.05-0.2 mg PO OD)
- elderly patients and those with CAD: start at 0.025 mg daily and increase gradually (start low, go slow)
- after initiating L-thyroxine, TSH needs to be evaluated in 6 weeks; doses adjusted until TSH returns to normal reference range
- once maintenance dose achieved, follow-up with patient annually
- secondary/tertiary hypothyroidism:
 - need to rule out and/or treat adrenal insufficiency first
 - monitor via measurement of TSH and also T₄

CONGENITAL HYPOTHYROIDISM

- see [Pediatrics](#), P30

Hashimoto's Thyroiditis

- most common form of primary hypothyroidism in North America
- chronic autoimmune thyroiditis characterized by both cellular and humoral factors in the destruction of thyroid tissue
- two major forms: goitrous and atrophic; both forms share same pathophysiology but differ in the extent of lymphocytic infiltration, fibrosis, and thyroid follicular cell hyperplasia
- goitrous variant usually presents with a rubbery goitre and euthyroidism, then hypothyroidism becomes evident
 - associated with fibrosis
- atrophic variant patients are hypothyroid from the start
 - associated with thyroid lymphoma

Etiology and Pathophysiology

- defect in clone of T-suppressors leads to cell-mediated destruction of thyroid follicles
- B lymphocytes produce antibodies against thyroid components including thyroglobulin, thyroid peroxidase, TSH receptor, Na/I symporter

Risk Factors

- female gender
- genetic susceptibility: increased frequency in patients with Down's syndrome, Turner's syndrome, certain HLA alleles, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
- family Hx or personal Hx of other autoimmune diseases
- cigarette smoking
- high iodine intake
- stress and infection

Investigations

- high TSH, low T₃, low T₄
- presence of thyroid peroxidase and thyroglobulin antibodies in serum

Treatment

- if hypothyroid, replace with L-thyroxine (analog of T₄)

Myxedema Coma

Definition

- severe hypothyroidism complicated by trauma, sepsis, cold exposure, MI, inadvertent administration of hypnotics or narcotics, and other stressful events – this is a MEDICAL EMERGENCY!
- rare, but serious mortality when it occurs (up to 60%, despite therapy)

Clinical Features

- hypothermia, hyponatremia, hypoglycemia, hypotension, bradycardia, hypoventilation, generalized edema, unresponsiveness

Investigations

- decreased free T₃ and T₄, increased TSH, decreased glucose
- check ACTH and cortisol for evidence of adrenal insufficiency

Treatment

- aggressive treatment required
- ABCs – patient should be in ICU setting
- corticosteroids (due to the possibility of concomitant adrenal insufficiency): hydrocortisone 100 mg q8h
- L-thyroxine 0.2-0.5 mg IV loading dose, then 0.1 mg IV OD until oral therapy tolerated
- supportive measures: mechanical ventilation, fluids, vasopressor drugs, passive rewarming, IV dextrose
- monitor for arrhythmia

Sick Euthyroid Syndrome (SES)

Definition

- changes in circulating thyroid hormones amongst patients with serious illness, trauma, or stress
- not due to intrinsic thyroid or pituitary disease

Pathophysiology

- the abnormalities in SES include alterations in
 - peripheral transport and metabolism of thyroid hormone
 - regulation of TSH secretion
 - thyroid function itself

Labs

- initially decreased free T_3 followed by decreased TSH and finally decreased free T_4

Etiology**Table 23. Etiology of SES**

Types of SES	Features
Normal-T_4 variant	<ul style="list-style-type: none"> Low free T_3, normal free T_4, normal TSH Proposed mechanism: inhibition of peripheral 5' monodeiodination of T_4 to T_3
Low-T_4 variant	<ul style="list-style-type: none"> Low free T_3, low free T_4, normal or low TSH Low T_4 likely due to inhibited T_4 binding to serum proteins and accelerated metabolic clearance Poorer prognosis

Treatment

- treat the underlying disease; thyroid hormone replacement worsens outcomes

Non-Toxic Goitre

Definition

- generalized enlargement of the thyroid gland in a euthyroid individual that does not result from inflammatory or neoplastic processes

Pathophysiology

- the appearance of a goitre is more likely during adolescence, pregnancy, and lactation because of increased thyroid hormone requirements
 - early stages: goitre is usually diffuse
 - later stages: multinodular non-toxic goitre with nodule, cyst formation and areas of ischemia, hemorrhage, and fibrosis

Etiology

- iodine deficiency or excess
- goitrogens: brassica vegetables (turnip, cassava)
- drugs: iodine, lithium, para-aminosalicylic acid
- any disorder of hormone synthesis with compensatory growth
- peripheral resistance to thyroid hormone

Treatment

- remove goitrogens
- suppression with L-thyroxine (rarely done)
- surgery may be necessary for severe compressive symptoms

Complications

- compression of neck structures causing stridor, dysphagia, pain, and hoarseness
- multinodular goitre may become autonomous leading to toxic multinodular goitre and hyperthyroidism

Thyroid Nodules

Definition

- clearly defined discrete mass, separated from the thyroid parenchyma
- palpable nodules are found in approximately 4% of the population
- M:F = 1:4

Etiology

- benign tumours (e.g. follicular adenoma)
- thyroid malignancy
- hyperplastic area in a multinodular goitre
- cyst: true thyroid cyst, area of cystic degeneration in a multinodular goitre

Investigations

- thyroid ultrasound to determine size and characteristic (cystic versus solid)
- thyroid function tests
- thyroid scan only if TSH is low to determine if nodule is hot (i.e. significant ^{131}I uptake into nodule) which signifies very low malignant potential
- FNA for all nodules >1-1.5 cm

Thyroid Malignancies

- see Otolaryngology, OT37

Adrenal Cortex

Adrenocorticotropin Hormone (ACTH)

- a polypeptide secreted in a pulsatile fashion from the anterior pituitary with diurnal variability (peak: 0200-0400; trough: 1800-2400)
- part of a prohormone (pro-opiomelanocorticotropin, POMC) which contains alpha, beta and gamma melanocyte-stimulating hormones, beta-endorphin and beta-lipotropin as well as ACTH
- secretion of ACTH regulated by corticotropin-releasing hormone (CRH) and arginine vasopressin
- stimulates growth of adrenal cortex and secretion of its hormones via cAMP
- stimulates release of glucocorticoids, androgens and, to a limited extent, mineralocorticoids
- some melanocyte stimulating activity

Adrenocortical Hormones

- all derived from cholesterol
 - mineralocorticoids (aldosterone) from zona glomerulosa
 - glucocorticoids (cortisol) from zona fasciculata
 - androgens (DHEA, androstenedione) from zona reticularis

Aldosterone

- a mineralocorticoid, which regulates extracellular fluid (ECF) volume through Na (and Cl^-) retention and K (and H^+) excretion (by stimulation of distal tubule Na/K ATPase)
- regulated by the renin-angiotensin-aldosterone system
- negative feedback to juxtaglomerular apparatus (JGA) by long loop (aldosterone via volume expansion) and short loop (angiotensin II via peripheral vasoconstriction)

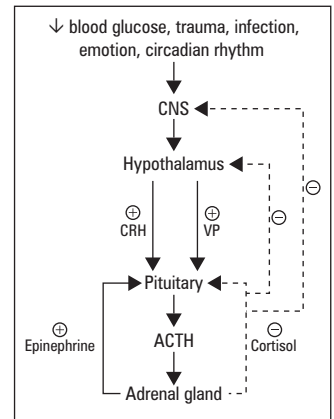


Figure 9. Regulation of CRH-ACTH-Adrenal Gland Axis

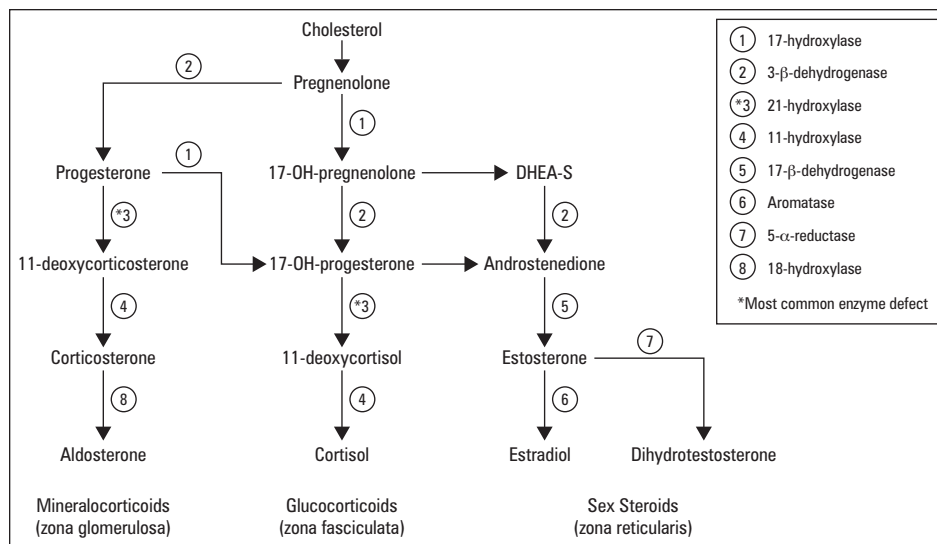
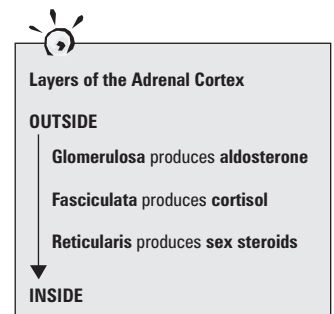


Figure 10. Pathways of Major Steroid Synthesis in the Adrenal Gland and their Enzymes



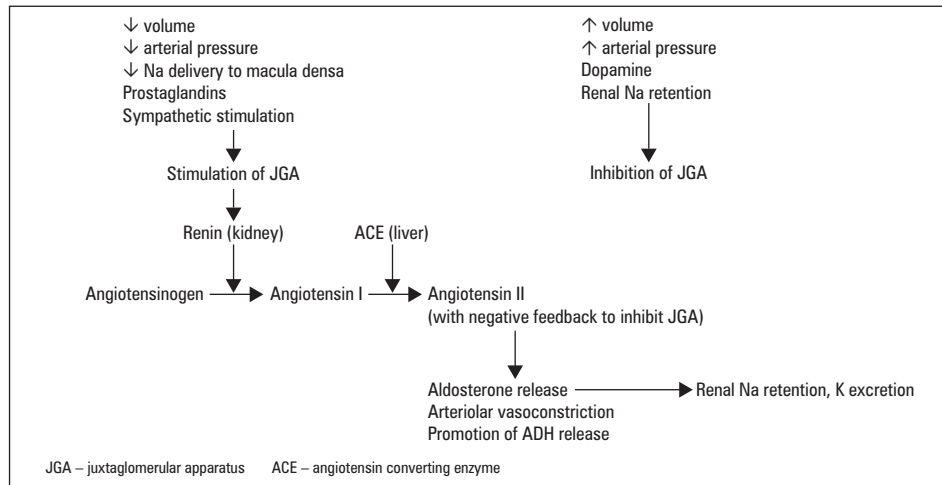


Figure 11. Renin-Angiotensin-Aldosterone Axis, (see [Nephrology](#))

Cortisol

Table 24. Physiological Effects of Glucocorticoids

Stimulatory Effects	Inhibitory Effects
Stimulate hepatic glucose production (gluconeogenesis)	Inhibit bone formation; stimulate bone resorption
Increase insulin resistance in peripheral tissues	Inhibit fibroblasts, causing collagen and connective tissue loss
Increase protein catabolism	Suppress inflammation; impair cell-mediated immunity
Stimulate leukocytosis and lymphopenia	Inhibit growth hormone axis
Increase cardiac output, vascular tone + Na retention	Inhibit reproductive axis
Increase PTH release, urine calcium excretion	Inhibit vitamin D ₃ and inhibit calcium uptake

Androgens

- sex steroids regulated by ACTH; primarily responsible for adrenarche (growth of axillary and pubic hair)
- principal adrenal androgens are dihydroepiandrosterone (DHEA), androstenedione and 11-hydroxyandrostenedione
- proportion of total androgens (adrenal to gonadal) increases in old age

Tests of Adrenocortical Function

Table 25. Markers of Adrenocortical Function

Plasma cortisol	Diurnal variation (random level less useful) Response to stimulation or suppression more informative
24 hour urinary free cortisol	Correlates well with secretory rates Good screening test for adrenal hyperfunction
Serum morning ACTH	High in primary adrenal insufficiency Low in secondary adrenal insufficiency
Serum DHEA-S	The main adrenal androgen

Dexamethasone (DXM) Suppression Tests (DST)

- gold standard to determine presence and etiology of hypercortisolism
- principle: DXM suppresses pituitary ACTH, so plasma cortisol should be lowered by negative feedback if HPA axis were normal
- single dose DST: screening test
 - DXM 1 mg given at 2300h would suppress pituitary ACTH production in healthy individuals, so that the normal 0800h peak of plasma cortisol would fail to develop
 - 95% of Cushing's syndrome patients would fail to suppress
 - <20% false positive results due to obesity, depression, alcohol, other medications
- confirmatory tests
 - low dose DST: 0.5 mg DXM q6h for 48 hours, then 24 hour urinary free cortisol (UFC)
 - ♦ normally, UFC level would be reduced to <54 nmol/day (149 µg/d)
 - high dose DST (8 mg/day): 70-80%
 - ♦ suppressed UFC: adrenal cortex hyperplasia due to hypersecretion of pituitary ACTH
 - ♦ no change in UFC or serum cortisol: adrenal cortisol-producing adenoma/carcinoma
 - however, 30-40% of ectopic ACTH tumours may partially suppress UFC
- plasma ACTH assay supplements DST for differentiation of the various etiologies of Cushing's

Short Cosyntropin Stimulation Test (ACTH analogue)

- for diagnosing adrenal insufficiency; dexamethasone does not interfere with this assay
- give 250 µg cosyntropin IM or IV then measure serum cortisol and ACTH at baseline, and cortisol at 0, 30 and 60 minutes
- physiological response: increase in plasma cortisol level by >250-500 µmol/L or doubling of baseline and an absolute level of >550 µmol/L (rules out primary adrenal insufficiency)
- inappropriate response: inability to stimulate increased plasma cortisol

Hyperaldosteronism

Table 26. Hyperaldosteronism

	Primary Hyperaldosteronism (PH)	Secondary Hyperaldosteronism (SH)
Definition	• Diastolic hypertension without edema	High aldosterone in response to activation of RAAS
Etiology	<ul style="list-style-type: none"> • Aldosterone-producing adrenal adenoma (Conn's syndrome) (75%) • Bilateral adrenal hyperplasia (25%) <ul style="list-style-type: none"> – Idiopathic – Glucocorticoid-remediable aldosteronism • Adrenal carcinoma (1%) • Adrenal enzyme defect/deficiency <ul style="list-style-type: none"> – 11β-HSD type II – 11β-hydroxylase – 17α-hydroxylase 	<ul style="list-style-type: none"> • Renin-producing tumour (rare) • Renal artery stenosis (renovascular hypertension) • CHF, cirrhosis, nephrotic syndrome • Diuretic/laxative abuse • Bartter's syndrome
Common Clinical Features	<ul style="list-style-type: none"> • Hypertension refractory to standard treatment • Polyuria, polydipsia, nocturia • Fatigue, weakness, paresthesia, headache; severe cases with tetany, intermittent paralysis • Labs: low K, high Na, low Mg, alkalosis, salt craving (also measure 24 hr metanephrines and catecholamines to r/o pheo) • Normal K, low Na in SH (low effective circulating volume leads to ↑ ADH release) 	
Diagnosis	<ul style="list-style-type: none"> • ↓ renin, ↑ aldosterone (>15 ng/dl) • Plasma aldosterone:renin ratio >20 ng/dL (normal ≤10 ng/dL) • Confirmatory tests: eaptopril suppression test, 24 h urine aldosterone, salt loading test • If suspecting adenoma: postural stimulation test, furosemide stimulation test, CT adrenal 	<ul style="list-style-type: none"> • ↑ renin, ↑ aldosterone • Aldosterone: renin ≤10 ng/dL
Treatment	<ul style="list-style-type: none"> • Medical tx for adrenal hyperplasia <ul style="list-style-type: none"> – Spironolactone, amiloride • Surgical removal for adrenal adenoma 	• Treat underlying cause

Cushing's Syndrome

**Definition**

- results from chronic glucocorticoid excess (endogenous or exogenous sources)

Etiology

- ACTH-dependent (85%) – bilateral adrenal hyperplasia and hypersecretion due to:
 - ACTH-secreting pituitary adenoma (Cushing's disease; 80% of ACTH-dependent)
 - ectopic ACTH-secreting tumour (e.g. small cell lung carcinoma, bronchial, carcinoid, pancreatic islet cell, pheochromocytoma or medullary thyroid tumours)
- ACTH-independent (15%)
 - long-term use of exogenous glucocorticoids (10 mg/d for >3 weeks)
 - primary adrenocortical tumours: adenoma and carcinoma (uncommon)
 - bilateral adrenal nodular hyperplasia
 - major depression and alcoholism

Clinical Features

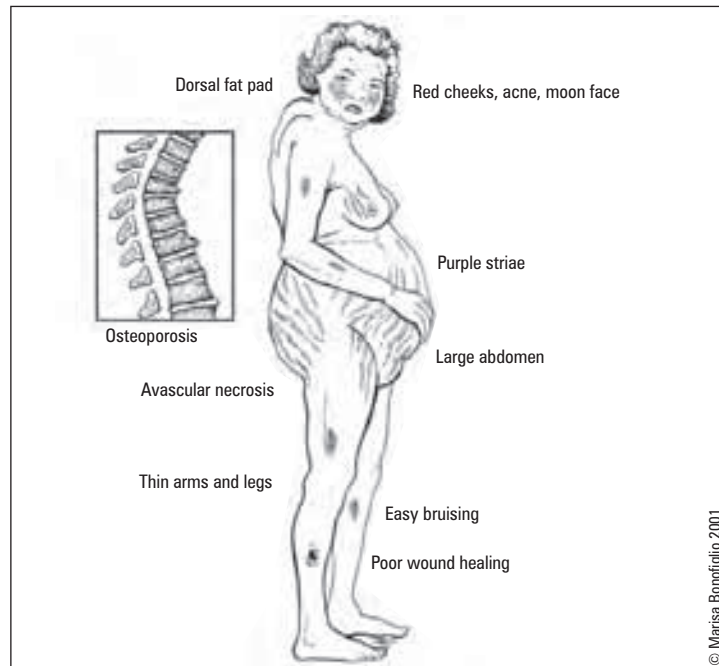


Figure 12. Clinical Features of Cushing's Syndrome

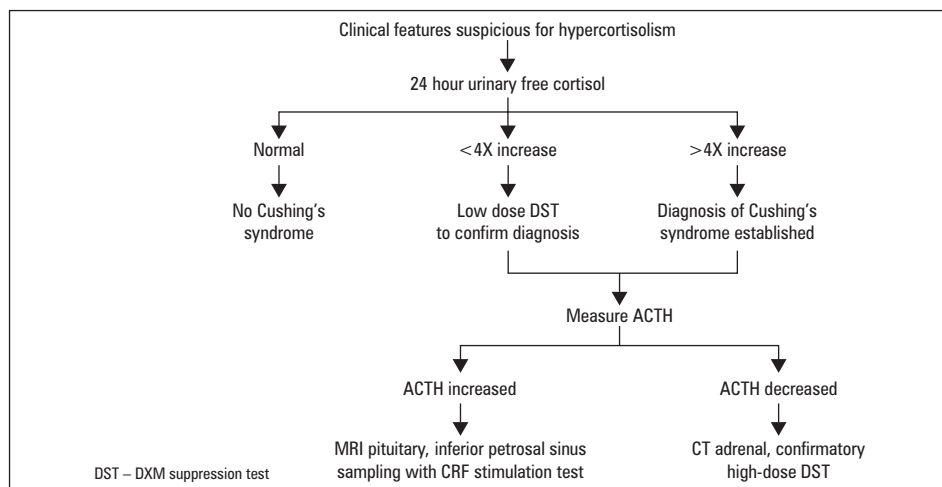


Figure 13. Hypercortisolism: Algorithm for Diagnosis

Treatment

- pituitary
 - trans-sphenoidal resection, with glucocorticoid supplement peri- and post-operatively
 - irradiation: only 50% effective, with significant risk of hypopituitarism
- adrenal
 - adenoma: unilateral adrenalectomy (curative)
 - carcinoma: palliative (frequent metastases, poor prognosis); adjunctive chemotherapy often not useful
 - medical treatment: mitotane, ketoconazole to reduce cortisol
- ectopic ACTH tumour – usually bronchogenic cancer (paraneoplastic syndrome)
 - chemotherapy/radiation for primary tumour
 - agents blocking adrenal steroid synthesis: metyrapone or ketoconazole
 - poor prognosis

Congenital Adrenal Hyperplasia

- see [Pediatrics](#), P32

Hyperandrogenism

Definition

- state of having excessive secretion of adrenal androgens (DHEA, DHEA sulfate)

Etiology and Pathophysiology

Table 27. Etiology of Hyperandrogenism

Constitutional/Familial	Family history, predisposing ethnic background Premature adrenarche
Medications	Anabolic steroids, ACTH, androgens, progestational agents
Androgen-mediated	
Ovarian	PCOS (see Gynecology , GY23) Ovarian hyperthecosis Theca cell tumours Pregnancy: placental sulfatase/aromatase deficiency
Adrenal	Congenital adrenal hyperplasia (CAH, late-onset CAH) Tumours (adenoma, carcinoma)
Pituitary	Cushing's disease – high ACTH Hyperprolactinemia

Clinical Features

Hirsutism

- male pattern growth of androgen-dependent terminal body hair in women: back, chest, upper abdomen, face, linea alba

Virilization

- masculinization: hirsutism, temporal balding, clitoral enlargement, deepening of voice, acne
- increase in musculature

Defeminization

- loss of female secondary sex characteristics (i.e. amenorrhea, ↓ breast size, infertility)

Males

- minimal effects on hair, muscle mass, etc.
- inhibition of gonadotropin secretion may cause reduction in testicular size, testicular testosterone production and spermatogenesis

Investigations

- increased testosterone
- increased LH/FSH, commonly in PCOS >2.5
- DHEA-S as measure of adrenal androgen production
- 17-OH progesterone is elevated in CAH due to 21-OH deficiency
- CT/MRI of adrenals (identify tumours)

Treatment

- discontinue causative medications
- oral contraceptives (e.g. cyproterone acetate – blocks androgen receptor; found in Diane 35®)
- spironolactone – acts as peripheral androgen antagonist
- cosmetic therapy
- low dose glucocorticoid ± mineralocorticoid if CAH suspected
- surgical resection of adrenal tumour



Two Conditions that do NOT Represent True Hirsutism

1. Androgen-independent hair (e.g. lanugo hair)
2. Drug-induced hypertrichosis (e.g. phenytoin, diazoxide, cyclosporine, minoxidil)

Adrenocortical Insufficiency

PRIMARY (ADDISON'S DISEASE)

Etiology

Table 28. Etiology of Primary Adrenocortical Insufficiency

Autoimmune (70-90%)	Isolated adrenal insufficiency Polyglandular autoimmune syndrome type I & II
Infection	TB (7-20%) (most common in developing world) Fungal: histoplasmosis, paracoccidioidomycosis HIV, CMV Syphilis African trypanosomiasis
Infiltrative	Metastatic cancer (lung>stomach>esophagus>colon>breast); lymphoma Sarcoidosis, amyloidosis, hemochromatosis
Vascular	Bilateral adrenal hemorrhage Sepsis (meningococcal, <i>Pseudomonas</i>) Coagulopathy in adults or Waterhouse-Friderichsen syndrome in children Thrombosis, embolism, adrenal infarction
Drugs	Inhibit cortisol: ketoconazole, megestrol acetate Increase cortisol metabolism: rifampin, phenytoin, barbituates, heparin, coumadin
Others	Adrenoleukodystrophy Congenital adrenal hypoplasia (impaired steroidogenesis) Familial glucocorticoid deficiency or resistance

- autoimmune etiology most common in developed world
 - antibodies often directed against adrenal enzymes and 3 zones of cortex

SECONDARY ADRENOCORTICAL INSUFFICIENCY

- inadequate pituitary ACTH secretion
- multiple etiologies (see *Hypopituitarism*, E19), including withdrawal of exogenous steroids that suppress pituitary ACTH production

Clinical Features

Table 29. Clinical Features of Primary and Secondary Adrenal Insufficiency (AI)

	Primary AI (Addison's or Acute AI)	Secondary AI
Skin and mucosa	Dark (palmar crease, extensor surface)	Pale
Potassium	High	Normal
Sodium	Low	Normal or Low
Metabolic acidosis	Present	Absent
Associated diseases	Primary hypothyroidism, type 1 diabetes, vitiligo, neurological deficits	Central hypogonadism or hypothyroidism, growth hormone deficiency, diabetes insipidus, headaches, visual abnormalities
Associated symptoms	Weakness, fatigue, weight loss, hypotension, salt craving, postural dizziness, myalgia, arthralgia, GI: nausea, vomiting, abdominal pain, diarrhea	NO hyperpigmentation NO salt craving GI less common
Diagnostic test	High morning plasma ACTH High 2 hour upright plasma renin	Low morning plasma ACTH Low 2 hour upright plasma renin

Adapted from: Salvatori, R. *JAMA* 2005;294:2481-2488.

Treatment

- acute condition – can be life-threatening
 - IV NS or D5W/NS in large volumes (2-3 L)
 - hydrocortisone 100 mg IV q6-8h for 24h, then gradual tapering
 - identify and correct precipitating factors
- maintenance
 - hydrocortisone 15-20 mg PO qam and 5-10 mg qpm (4:00 pm)
 - Florinef® (fludrocortisone, synthetic mineralocorticoid) 0.05-0.2 mg PO daily if mineralocorticoid deficient (maintain renin between 1-3 ng/ml/hr)
 - increase dose of steroids 2-3 fold for a few days during moderate-severe illness (vomiting, fever)
 - major stress (surgery, trauma) requires 150-300 hydrocortisone IV daily divided into 3 doses
 - medical alert bracelet and instructions for emergency hydrocortisone IM injection

Adrenal Medulla

Catecholamine Metabolism

- catecholamines are synthesized from tyrosine in postganglionic sympathetic nerves and chromaffin cells of adrenal medulla
- predominant adrenal catecholamine = epinephrine (adrenaline)
- predominant peripheral catecholamine = norepinephrine (noradrenaline)



ABC of Adrenaline
Adrenaline activates
Beta-receptors, increasing
Cyclic AMP

Pheochromocytoma

Definition

- rare catecholamine secreting tumour derived from chromaffin cells of the sympathetic system

Epidemiology

- most commonly a single tumour of adrenal medulla
- 10% extra-adrenal (95% of which are intra-abdominal), 10% multiple tumours, 10% malignant, 10% familial
- rare cause of hypertension (<0.2% of all hypertensives)
- curable if recognized and properly treated, but fatal if not

Etiology and Pathophysiology

- most cases sporadic (80%)
- familial: associated with multiple endocrine neoplasia II (MEN II) (50%), von Hippel-Lindau (10-20%), paraganglioma (20%), or neurofibromatosis type 1 (NF I) (0.1-5.7%)
- tumours, via unknown mechanism, able to synthesize and release excessive catecholamines

Clinical Features

- 50% suffer from paroxysmal HTN; the rest have sustained HTN
- classic triad: episodic "pounding" headache, palpitations/tachycardia, diaphoresis
- other symptoms: tremor, anxiety, chest or abdominal pain, nausea/vomiting, visual blurring, weight loss, polyuria, polydipsia
- other signs: orthostatic hypotension, papilledema, increased ESR, hyperglycemia, dilated cardiomyopathy
- symptoms may be triggered by stress, exertion, anesthesia, abdominal pressure, certain foods (especially tyramine containing foods)



Classic Triad of PHEOchromocytoma
Palpitations
Headache
Episodic sweating

Investigations

- urine catecholamines
 - increased catecholamine metabolites (metanephrines) and free catecholamines
 - total metanephrine (most sensitive) >6.5 $\mu\text{mol/day}$ (1.2 mg/day)
- plasma catecholamines
 - >2000 pg/ml (11.8 mmol/L) diagnostic
 - >950 pg/ml (5.6 mmol/L) suggestive; proceed to clonidine suppression test (rarely done)
 - elevated plasma epinephrine unsuppressed by clonidine (central alpha-adrenergic) is diagnostic
- CT abdomen
 - if CT is negative, meta-iodo-benzoguanidine (MIBG) scintigraphy, Octreoscan, or MRI may be helpful

Treatment

- adequate pre-operative preparation
- alpha-blockade for BP control – phenoxybenzamine (14-21 days pre-operative), IV phentolamine (peri-operative)
- beta-blockade for HR control – propranolol (initiate only after adequate alpha-blockade)
- metyrosine (catecholamine synthesis inhibitor) + phenoxybenzamine or prazosin
- volume restoration with vigorous salt-loading
- surgical removal of tumour with careful pre-operative and post-operative ICU monitoring
- rescreen urine one month post-operatively

Multiple Endocrine Neoplasm (MEN)

- neoplastic syndromes involving multiple endocrine glands
- tumours of neuroectodermal origin
- autosomal dominant inheritance with variable penetrance
- genetic screening for RET proto-oncogene on chromosome 10 has long-term benefit
 - early cure and prevention of medullary thyroid cancer

Table 30. MEN Classification

Type	Chromosome Implicated	Tissues Involved	Clinical Manifestations
MEN I Wermer's Syndrome	11 (PYGM gene)	Pituitary Parathyroid Entero-pancreatic endocrine	Ant. pituitary adenoma, often non-secreting but may secrete GH and PRL Primary hyperparathyroidism from hyperplasia Pancreatic islet cell tumours Gastrinoma (peptic ulcers) Insulinomas (hypoglycemia) VIPomas (secretory diarrhea)
MEN II 3 Distinct Syndromes	10 (RET proto-oncogene)		
1. Ila Sipple's Syndrome		Thyroid Adrenal medulla Parathyroid Skin	Medullary thyroid cancer (MTC) (>90%) Pheochromocytoma (40-50%) 1° parathyroid hyperplasia (10-20%) Cutaneous lichen amyloidosis
2. Familial Medullary Thyroid Ca. (a variant of Ila)		Thyroid	MTC without other clinical manifestations of MEN Ila or IIb
3. IIb		Thyroid Adrenal medulla Neurons MSK GI	MTC: most common component, more aggressive and earlier onset than MEN Ila Pheochromocytoma Mucosal neuroma, intestinal ganglioneuromas Marfanoid habitus (no aortic abnormalities) Chronic constipation Megacolon

History

- MEN I
 - symptoms of hyperparathyroidism, gastrinoma (abdominal pain, diarrhea, peptic ulcer disease), and insulinoma
- MEN II
 - family history of MEN syndromes
 - symptoms related to medullary thyroid cancer (MTC), hyperparathyroidism, or pheochromocytoma
 - scaly skin rash (cutaneous lichen amyloidosis in MEN Ila)

Clinical Features

- clinical picture depends on the endocrine organs involved and the hormones secreted
- MEN I
 - hyperparathyroidism – nephrolithiasis, bone abnormalities, MSK complaints
 - generalized weakness, and alterations of mental status in severe hypercalcemia
 - gastrinoma – upper abdominal pain due to peptic ulcers and esophagitis
 - glucagonoma – rash, anorexia, anemia, diarrhea, glossitis
 - pituitary tumour – headache, visual-field defects, prolactinoma (erectile dysfunction, decreased libido, amenorrhea, galactorrhea), acromegaly
 - carcinoid syndrome – flushing, diarrhea, bronchospasm
- MEN II – physical signs are variable and often subtle
 - MTC – neck mass or thyroid nodule; non-tender, anterior neck lymph nodes
 - pheochromocytoma – elevated BP and HR



MEN I – Wermer's Syndrome Affects the 3 Ps

Pituitary
Parathyroid
Pancreas

Investigations

- MEN I
 - laboratory
 - ♦ gastrinoma – elevated serum gastrin level (>200 ng/mL) after IV injection of secretin
 - ♦ insulinoma – reduced fasting blood glucose (hypoglycemia)
 - ♦ glucagonoma – elevated blood glucose and glucagon levels
 - ♦ pituitary tumours – assess GH and prolactin levels
 - ♦ hyperparathyroidism – PTH levels; bone density scan (DEXA)
 - imaging
 - ♦ MRI for pituitary tumours, gastrinoma, insulinoma
- MEN II
 - laboratory
 - ♦ genetic screening for RET mutations in all index patients
 - if a mutation is identified, screen family members who are at risk
 - ♦ calcitonin levels, urine catecholamines, vanillylmandelic acid and metanephrine screen (pheochromocytoma); serum Ca and PTH levels (hyperparathyroidism)
 - ♦ pentagastrin \pm calcium stimulation test if calcitonin level is within reference range
 - imaging
 - ♦ CT or MRI for imaging of the adrenal glands
 - ♦ metaiodobenzylguanidine (MIBG) scan for pheochromocytoma
 - ♦ radionuclide scanning for determining the extent of metastasis
 - ♦ octreoscan for examining the spread of MTC
 - ♦ FNA for thyroid nodules

Treatment

- MEN I
 - surgery is indicated for hyperparathyroidism, insulinoma, glucagonoma, pituitary tumours (trans-sphenoidal approach with external radiation when medical treatment fails)
 - ♦ proton pump inhibitor (PPI) for acid hypersecretion in gastrinoma
 - ♦ bromocriptine or other dopamine agonists to suppress prolactin secretion
 - ♦ somatostatin for symptomatic carcinoid tumours
- MEN II
 - surgery for MEN IIa
 - pre-operative treatment
 - ♦ prostaglandin inhibitors to alleviate diarrhea associated with thyroid cancer
 - ♦ alpha-blocker for at least 2 weeks for pheochromocytoma
 - ♦ hydration for hypercalcemia
 - if remains severely hypercalcemic, consider calcitonin or bisphosphonates
 - post-operative treatment
 - ♦ hormone replacement following total thyroidectomy and bilateral adrenalectomy
 - ♦ calcium supplement and/or vitamin D for post-op hypoparathyroidism

Calcium Homeostasis



- normal total serum Ca: 2.25-2.62 mmol/L (9.0-10.5 mg/dL)
- ionic/free Ca levels: 1.15-1.31 mmol/L (4.6-5.25 mg/dL)
- serum Ca is about 50% protein bound (mostly albumin)
- regulated mainly by two factors: parathyroid hormone (PTH) and vitamin D
- actions mainly on 3 organs: GI tract, bone, and kidney

Parathyroid Hormone (PTH)

- secretion increased by low serum Ca and inhibited by chronic, low serum Mg
- not influenced directly by PO_4 (except by PO_4 effect on the ionic calcium levels)

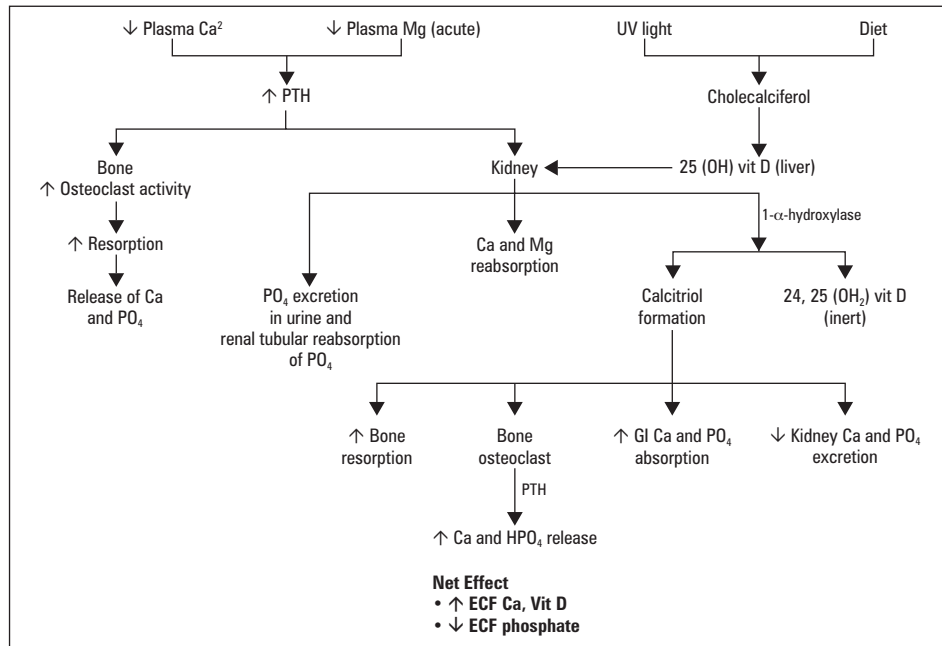


Figure 14. Parathyroid Hormone (PTH) Regulation

Vitamin D

- necessary for Ca and PO₄ absorption from GI tract
- cholecalciferol formed in the skin by the action of UV light

Calcitonin

- polypeptide secreted by thyroid C cells
- secretion enhanced by Ca, GI hormones, pentagastrin
- major actions
 - ↓ osteoclastic bone resorption (pharmacological effect)
 - ↑ renal PO₄ and Na clearance
 - acute net effect: ↓ serum Ca when given in pharmacologic doses

Magnesium

- major intracellular divalent cation
- Ca is reabsorbed from the kidney with Mg
 - thus Ca balance is difficult to maintain in Mg deficiency

Phosphorus

- intracellular cation
- found in all tissues and necessary for most biochemical processes as well as bone formation

Table 31. Summary of Effects

Hormone	Net Effect
Parathyroid Hormone (PTH)	Increased Ca Increased Vit D Decreased PO ₄
Vitamin D	Increased Ca Increased PO ₄
Calcitonin (in pharmacologic doses)	Decreased Ca



Pseudohypercalcemia: increased protein binding leading to an elevation in serum total Ca without a rise in the ionized/free form, e.g. hyperalbuminemia from severe dehydration.



Corrected Ca (mmol/L) = measured Ca + 0.02 (40 – albumin)

For every decrease in albumin by 10, increase in Ca by 0.2

Benign (less likely malignant):
Ca < 2.75 mmol/L (11 mg/dL)

Pathologic (more likely malignant):
Ca > 3.25 mmol/L (13 mg/dL)

Hypercalcemia

Definition

- total corrected serum Ca > 2.62 mmol/L (10.5 mg/dL) OR ionized Ca > 1.35 mmol/L (5.4 mg/dL)

Approach to Hypercalcemia (Figure 15)

1. Is the patient hypercalcemic? (correct for albumin – see sidebar)
2. Is the PTH high/normal or low?
3. If PTH is low, is phosphate high/normal or low? If phosphate is high/normal are the level of vitamin D metabolites high or low?

Increased Ca with High/Normal PTH		
Etiology	Risk Factors	Approach
Primary Hyperparathyroidism (#1 cause of hypercalcemia in outpatients) <ul style="list-style-type: none"> Solitary Adenoma 81% Hyperplasia 15% Carcinoma 4% MEN I and IIa 	<ul style="list-style-type: none"> Positive FMHx Hx of MEN/IIa Hx of childhood H+N radiation Postmenopausal women Normal physical exam 	<ul style="list-style-type: none"> Px: <ul style="list-style-type: none"> 50% asymptomatic (esp. with prolonged disease) Renal calculi, neuromuscular disease, low BMD Ix: serum Ca, PO_4, PTH, Imaging for renal calculi and osteoporosis Tx: surveillance vs. surgery
Tertiary Hyperparathyroidism	<ul style="list-style-type: none"> Renal failure Previous renal transplant 	<ul style="list-style-type: none"> Increased PTH after prolonged secondary hyperparathyroidism
Familial Hypocalciuric Hypercalcemia (FHH) <ul style="list-style-type: none"> Mutation in Ca sensing receptor gene → inappropriate PTH secretion and tubal Ca reabsorption 	<ul style="list-style-type: none"> Asymptomatic Hypocalciuric Positive FMHx (autosomal dominant) 	<ul style="list-style-type: none"> Ix: normal/mildly elevated PTH, low urinary Ca, normal 25-OH Vit D
Drug Induced <ul style="list-style-type: none"> Increased set point where PTH secretion is suppressed 	<ul style="list-style-type: none"> Lithium 	<ul style="list-style-type: none"> Ix: increased serum Ca with hypocalciuria
Increased Ca with Low PTH		
<pre> graph TD PTH[↓ PTH] --> Phosphate[↑ or normal phosphate] PTH --> Phosphate2[↓ phosphate related to ↑ PTHrP] Phosphate --> VitD[Vit D related] VitD --> CalcitriolVitD[↑ Calcitriol or Vit D] VitD --> Calcitriol[↑ Calcitriol] CalcitriolVitD --> HypervitaminosisD[Hypervitaminosis D: excessive intake of vit D or its metabolites] Calcitriol --> GranulomatousDisease[Granulomatous disease e.g. TB, sarcoid, lymphoma (esp. Hodgkins) which causes extra-renal production of calcitriol by macrophages in the lung and lymph nodes. Excessive calcitriol intake] Phosphate2 --> HumoralMediation[Humoral mediation lung Ca, RCC, pheochromocytoma] HumoralMediation --> LowVitD[Low Vit D metabolites] LowVitD --> Immobilization[Immobilization Milk alkali syndrome hypercalcemia with alkalosis and renal failure Drugs: thiazide diuretics, CaCO3, theophylline, estrogen/tamoxifen Metastatic bone disease e.g. breast Ca mediated by Osteoclast Activating Factor High bone turnover e.g. hypervitaminosis A, thyrotoxicosis, Paget's disease] </pre>		

Figure 15. Differential Diagnosis of Hypercalcemia

Clinical Features

- symptoms depend on the absolute Ca value and the rate of its rise (may be asymptomatic)

Table 32. Symptoms of Hypercalcemia

Cardiovascular	GI	Renal	Rheumatological	MSK	Psychiatric	Neurologic
Hypertension	Constipation	Polyuria	Gout	Weakness	>3 mmol/L	Hypotonia
Arrhythmia	Anorexia	(Nephrogenic DI)	Pseudogout	Bone pain	(12 mg/dL)	Hyporeflexia
Short QT	Nausea	Polydipsia	Chondrocalcinosis	(bones)	Increased alertness	Myopathy
Deposition of Ca on valves, coronary arteries, myocardial fibres	Vomiting (groans)	Nephrolithiasis (stones)			Anxiety	Paresis
	PUD	Renal failure (irreversible)			Depression	
	pancreatitis				Cognitive dysfunction	
					Organic brain syndromes	
					>4 mmol/L (16 mg/dL)	
					Psychosis (moans)	

**** Hypercalcemia crisis (usually >4 mmol/L):** primary symptoms include oliguria/anuria and mental status changes (including somnolence and eventually coma) → this is a MEDICAL EMERGENCY and should be treated immediately!

Treatment

- treatment depends on the Ca level and the symptoms
- treat acute, symptomatic hypercalcemia aggressively



The most common cause of hypercalcemia in hospital is **malignancy-associated hypercalcemia**

- Usually occurs in the later stages of disease
- Most commonly seen in renal, breast, ovarian and squamous tumours, as well as lymphoma and multiple myeloma
- Mechanism: secretion of parathyroid hormone-related protein (PTHrP) which mimics PTH action by preventing renal calcium excretion and activating osteoclast-induced bone resorption

Primary hyperparathyroidism is the most common cause of hypercalcemia in healthy outpatients.



Differential Diagnosis of Hypercalcemia

1. Primary hyperparathyroidism
2. Malignancy: hematologic, humoral, skeletal metastases (>90% from 1 or 2)
3. Renal Disease: tertiary hyperparathyroidism
4. Drugs: calcium carbonate, milk-alkali syndrome, thiazide, lithium, theophylline, vitamin A/D intoxication
5. Familial hypocalciuric hypercalcemia
6. Granulomatous disease: sarcoidosis, TB
7. Thyroid disease: thyrotoxicosis
8. Adrenal disease: adrenal insufficiency, pheochromocytoma
9. Immobilization



Watch Out For:

- Volume depletion via diuresis
- Arrhythmias



The symptoms and signs of hypercalcemia include: **"Bones, stones, psychosis-based moans, and abdominal groans"**



Acute Management of Hypercalcemia/Hypercalcemic Crisis

1. Volume expansion (e.g. NS IV 300-500 cc/hr) – initial therapy
2. Calcitonin – transient, partial response
3. Bisphosphonate – treatment of choice
4. Corticosteroid – most useful in Vit D toxicity, granulomatous disease, some malignancies
5. Saline diuresis + loop diuretic (for volume overload) – temporary measure

Table 33. Treatment of Acute Hypercalcemia/Hypercalcemic Crisis

Increase Urinary Ca Excretion	Isotonic saline (4-5 L) ± loop diuretic (e.g. furosemide) but only if hypervolemic
Diminish Bone Resorption	Bisphosphonates (Tx of choice) <ul style="list-style-type: none"> • Inhibits osteoclastic bone resorption and promotes renal excretion of calcium • Acts rapidly but often transient response (decreased by 0.3-0.5 mmol/L (1.2-2.0 mg/dL) beginning within 4-6 hours) • Combination of calcitonin and steroids may prolong reduction in calcium • Tachyphylaxis may occur • Indicated in malignancy-related hypercalcemia, IV pamidronate is most commonly used 2-4 days until full effect but effect is long-lasting (2-4 weeks) Mithramycin (rarely used) – effective when patient cannot tolerate large fluid load <ul style="list-style-type: none"> ▪ Dangerous – hematotoxic and hepatotoxic
Decrease GI Ca Absorption	Corticosteroids in hypervitaminosis D and hematologic malignancies <ul style="list-style-type: none"> • Anti-tumour effects → decreased calcitriol production by the activated mononuclear cells in lung and lymph node • Slow to act (5-10 days); need high dose
Dialysis	
Chelation	EDTA or IV phosphate (rarely used) Oral phosphate in chronic hypercalcemia

Others

- prostaglandin inhibitors
- surgical treatment if indicated
- avoid immobilization



Hypocalcemia

Definition

- total corrected serum Ca <2.25 mmol/L (9.0 mg/dL)

Clinical Features

- most characteristic symptom is tetany

Differential Diagnosis of Tetany

- metabolic alkalosis (with hyperventilation)
- hypokalemia
- hypomagnesemia

Approach to Treatment

- correct underlying disorder
- mild/asymptomatic (ionized Ca >0.8 mmol/L, 3.2 mg/dL)
 - treat by increasing dietary Ca by 1000 mg/day
- acute/symptomatic hypocalcemia (ionized Ca <0.7 mmol/L, 2.8 mg/dL)
 - immediate treatment required
 - IV calcium gluconate 1-2 g in 10-20 mins followed by slow infusion if necessary
 - goal is to raise Ca to low normal range (2.0-2.1 mmol/L, 8.0-8.4 mg/dL) to prevent symptoms but allow maximum stimulation of PTH
- if PTH recovery not expected, requires long-term therapy with vitamin D and calcium
- do not correct hypocalcemia if it is suspected to be a transient response

Table 34. Clinical Features of Hypocalcemia

Acute Hypocalcemia	Chronic Hypocalcemia
Delirium	CNS: lethargy, seizures, psychosis, basal ganglia calcification, Parkinson's, dystonia,
Laryngospasm (with stridor)	hemiballismus, papilledema, pseudotumour cerebri
Paresthesia	CVS: prolonged QT interval
Hyperreflexia	GI: steatorrhea
Tetany	ENDO: impaired insulin release
Psychiatric Sx: emotional instability, anxiety and depression	SKIN: dry, scaling, alopecia, brittle and transversely fissured nails, moniliasis, abnormal dentition
Chvostek's sign (tap CNVII)	OCULAR: cataracts
Trousseau's sign (carpal spasm)	MSK: generalized muscle weakness and wasting



Signs and Symptoms of Acute Hypocalcemia

- **Paresthesias:** perioral, hands and feet
- **Chvostek's sign:** percussion of the facial nerve just anterior to the external auditory meatus elicits ipsilateral spasm of the orbicularis oculi or orbicularis oris muscles
- **Trousseau's sign:** inflation of a blood pressure cuff above systolic pressure for 3 minutes elicits carpal spasm and paresthesia

Approach to Hypocalcemia (Figure 16)

1. Is the patient hypocalcemic (correct for albumin)?
2. Is the PTH high or low?
3. If PTH is high, is phosphate low or normal?

Decreased Ca with Low PTH		
Iatrogenic Hypoparathyroidism	• Post-thyroidectomy, ¹³¹ I ablation, post surgical correction of primary hyperparathyroidism	
Primary Hypoparathyroidism	• Idiopathic/autoimmune hypoparathyroidism: DiGeorge syndrome, polyglandular autoimmune disease (acquired hypoparathyroidism ± adrenal insufficiency ± gonadal failure ± hypothyroidism and rarely hypopituitarism, diabetes insipidus, Type I DM) • Infiltrative diseases of parathyroid gland • HIV	
Secondary Hyperparathyroidism	Risk Factors • PT gland appropriately responds to low EC Ca, by ↑ absorption and ↑ bone resorption • Renal failure: low vit D synthesis • Low dietary Ca • GI malabsorption • Bisphosphonate use	Approach • Ix: increased PTH, normal/decreased serum Ca; renal function (Cr), Vit D/Ca sufficiency (25-OH Vit D, urinary Ca); GI w/u if high suspicion
Low Magnesium	• Under normal circumstances, low Mg stimulates PTH secretion • However, chronic low Mg is paradoxically associated with impaired PTH secretion • Low Mg levels also impair peripheral responsiveness to PTH • Drugs: antineoplastic agents (cisplatin, mithramycin) • Alcoholism	
Liver Dysfunction	• Hemochromatosis	
Pregnancy	• In pregnancy, there is a low total Ca due to hypoalbuminemia, but normal ionized level	
Decreased Ca with High PTH (Secondary Hyperparathyroidism)		
<div><div>↑ PTH</div><div><div>↓↓ phosphate</div><div>Vit D related</div><div><div>↓ Calcidiol</div><div>Decreased GI absorption (intake, liver/biliary) Phenytoin Nephrotic syndrome (lose Vit D binding protein)</div></div><div><div>↓ Calcitriol</div><div>Chronic renal failure Vit D dependent rickets type 1 (renal 1-alpha-hydroxylase deficiency)</div></div></div><div><div>Normal phosphate</div><div>Pseudohypoparathyroidism: PTH resistance secondary to G-protein deficiency Acute pancreatitis: release of pancreatic caldecrin decreases bone resorption Drugs: calcitonin, loop diuretics</div><div><div>↑ Calcitriol</div><div>Hereditary Vit D resistant rickets type II (receptor defect)</div></div></div></div>		

Figure 16. Etiology and Clinical Approach to Hypocalcemia

Hyperphosphatemia

Etiology

- increased intake
 - GI intake (rectal enema, GI bleeding)
 - IV phosphate load (K-Phos®, blood transfusion)
 - endogenous phosphate (tumour lysis syndrome, rhabdomyolysis, hemolysis)
- reduced renal clearance
 - ARF/CRF
 - hypoparathyroidism
 - acromegaly
 - tumour calcinosis (ability of kidney to specifically clear phosphate is defective)

Clinical Features

- non-specific, include ectopic calcification, renal osteodystrophy

Treatment

- low PO_4 diet, phosphate binders (e.g. CaCO_3)

Hypophosphatemia

Etiology

- inadequate intake
 - starvation
 - malabsorption (diarrhea, steatorrhea)
 - antacid use
 - alcoholism
- renal losses
 - hyperparathyroidism
 - diuretics
 - X-linked or AD hypophosphatemic rickets
 - Fanconi syndrome
- excessive skeletal mineralization
 - osteoblastic metastases
 - post parathyroidectomy (referred to as 'hungry bone syndrome')
- PO_4 shift into ICF
 - recovery from metabolic acidosis
 - respiratory alkalosis
 - starvation refeeding (stimulated by insulin)

Clinical Features

- non-specific (CHF, coma, hypotension, weakness)

Treatment

- treat underlying cause, supplement with oral PO_4 : 2-4 g/d divided bid-qid (start at 1000 mg/d to minimize diarrhea)

Hypermagnesemia

Etiology

- Mg-containing antacids given to those with severe renal failure
- IV administration of large doses of MgSO_4 (e.g. for pre-eclampsia; see [Obstetrics](#), OB14)

Clinical Features

- drowsiness, hyporeflexia, respiratory depression, decreased deep tendon reflexes

Treatment

- discontinue Mg-containing products

Hypomagnesemia

Etiology

- GI
 - starvation
 - malabsorption
 - vomiting
 - alcoholism
 - acute pancreatitis
- excess renal loss
 - 2° hyperaldosteronism due to cirrhosis and CHF
 - hyperglycemia
 - hypokalemia
 - hypercalcemia
 - diuretics

Clinical Features

- seizures, paresthesia, Chvostek and Trousseau signs

Treatment

- Mg IM/IV; cellular uptake of Mg is slow, therefore repletion requires sustained correction
- discontinue diuretics
 - in patients requiring diuretics, use a K-sparing diuretic to minimize magnesuria
- magnesium deficiency can aggravate potassium depletion by increasing distal potassium secretion, often refractory to treatment with potassium replacement
 - thus, important to check and correct magnesium levels prior to replacing potassium

Metabolic Bone Disease



Osteoporosis

Definition

- a condition characterized by decreased bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to bone fracture

ETIOLOGY AND PATHOPHYSIOLOGY

Primary Osteoporosis

- due to post-menopausal decline in estrogen, worsens with age

Secondary Osteoporosis

- gastrointestinal diseases
 - gastrectomy
 - malabsorption
 - chronic liver disease
- bone marrow disorders
 - multiple myeloma
 - lymphoma
 - leukemia
- endocrinopathies
 - Cushing's syndrome
 - hyperparathyroidism
 - hyperthyroidism
 - premature menopause
 - diabetes
- malignancy
 - breast cancer
 - prostate cancer
- drugs
 - corticosteroid therapy → second most common cause of osteoporosis
 - individuals receiving ≥ 7.5 mg of prednisone daily for over 3 months should be assessed for bone-sparing therapy
 - mechanism: increased resorption + decreased formation
 - phenytoin
 - chronic heparin therapy
 - androgen deprivation therapy
 - aromatase inhibitors
- others
 - rheumatologic disorders
 - rheumatoid arthritis
 - SLE
 - ankylosing spondylitis
 - renal disease
 - poor nutrition
 - immobilization

Risk Factors

Table 35. Risk Factors for Osteoporosis

Major Risk Factors	Minor Risk Factors
<ul style="list-style-type: none"> Age >65 years Vertebral compression fracture Fragility fracture after age 40 Family history of osteoporotic fracture (especially maternal hip fracture) Propensity to fall (general frailty, poor balance, decreased visual acuity) Osteopenia apparent on x-ray film 	Lifestyle/Diet <ul style="list-style-type: none"> Smoking Excessive alcohol intake Excessive caffeine intake Low dietary calcium intake Weight <57 kg Weight loss >10% of weight at age 25
Secondary to Medical Disease <ul style="list-style-type: none"> Malabsorption syndrome Primary hyperparathyroidism 	Secondary to Medical Disease <ul style="list-style-type: none"> Rheumatoid Arthritis Past history of clinical hyperthyroidism
Drugs <ul style="list-style-type: none"> Systemic glucocorticoid therapy >3 months duration 	Drugs <ul style="list-style-type: none"> Chronic anticonvulsant therapy Chronic heparin therapy
Hormonal Deficiency <ul style="list-style-type: none"> Early menopause (before age 45) Hypogonadism 	

Use of Calcium or Calcium in Combination with vitamin D Supplementation to Prevent Fractures and Bone Loss in People aged 50 years and older: A Meta-Analysis

Lancet 2007; 370:657-66

Purpose: To determine whether supplementation with calcium or calcium in combination with vitamin D reduces fractures of all types and percentage change of bone-mineral density from baseline.

Study Selection: Randomized trials that recruited people aged 50 years or older.

Results: In trials that reported fracture as an outcome (17 trials, n=52,625), treatment was associated with a 12% risk reduction in fractures of all types (risk ratio 0.88, 95% CI 0.83-0.95; p=0.0004). In trials that reported bone-mineral density as an outcome (23 trials, n=41,419), the treatment was associated with a reduced rate of bone loss of 0.54% (0.35-0.73; p<0.0001) at the hip and 1.19% (0.76-1.61%; p<0.0001) in the spine. The fracture risk reduction was significantly greater (24%) in trials in which the compliance rate was high (p<0.0001). The treatment effect was better with calcium doses of 1200 mg or more than with doses less than 1200 mg (0.80 vs. 0.94; p=0.006), and with vitamin D doses of 800 IU or more than with doses less than 800 IU (0.84 vs. 0.87; p=0.03).

Conclusion: Evidence supports the use of calcium, or calcium in combination with vitamin D supplementation, in the preventive treatment of osteoporosis in people aged 50 years or older. For best therapeutic effect, we recommend minimum doses of 1200 mg of calcium, and 800 IU of vitamin D (for combined calcium plus vitamin D supplementation).

Bisphosphonates in Osteoporosis

NEJM 1995; 333:1437-43

Study: Randomized, blinded, placebo-controlled trial (3 year follow-up).


Patients: 994 post-menopausal women (mean 64 yrs, 87% white) with low BMD (t=-2.5). Exclusions included hx of glucocorticoid use, other disorders of bone, active PUD, and renal or hepatic insufficiency.

Intervention: Alendronate 5 mg, 10 mg, 20 mg, or placebo, each once daily. All received calcium 500 mg/day. In the 3rd year, women in the 20 mg group were blindly switched to 5 mg.

Main outcomes: Change in BMD, new vertebral fractures, and height.

Results: Women in all 3 alendronate groups had significant increases in BMD, while those in the placebo group had significant decreases. Women taking alendronate had fewer new vertebral fractures (RRR 52%, NNT 34, 95% CI 16 to 518), and a lower mean loss of height (p=0.005). There were no significant differences between groups for non-vertebral fractures, adverse effects, or discontinuation rates.


Conclusion: In post-menopausal women with osteoporosis, alendronate increased BMD, and reduced the risk of new vertebral fractures.



Calcium Content in Common Foods

	Standard Portion	Calcium (elemental)
Milk and Milk products		
Cheese – Brick, Cheddar, Colby, Edam, Gouda	1.75 oz/50 g	353 mg
Cheese – cottage, creamed, 2%, 1%	1/2 cup/125 mL	87 mg
Cheese – Mozzarella	1.75 oz/50 g	269 mg
Cheese – Swiss, Gruyère	1.75 oz/50 g	493 mg
Ice cream	1/2 cup/125 mL	93 mg
Milk – powder, dry	3 tbsp/45 mL	159 mg
Milk – whole, 2%, 1%, skim	1 glass/250 mL	315 mg
Yogourt	175 g	320 mg
Meat, fish, poultry and alternatives		
Almonds	1/2 cup/125 mL	200 mg
Beans – cooked	1 cup/250 mL	90 mg
Sardines, with bones	8 small	153 mg
Sesame seeds	1/2 cup/125 mL	100 mg
Soybeans – cooked	1 cup/250 mL	175 mg
Tofu – with calcium sulfate	1/2 cup/125 mL	130 mg
Breads and cereals		
Bread – white/wheat	1 slice/30 g	25 mg
Muffin – bran	1/35 g	50 mg
Fruits and vegetables		
Broccoli – raw	1/2 cup/125 mL	38 mg
Figs – dried	10	270 mg
Orange	1 medium/180 g	52 mg
Combination dishes		
Baked beans – canned	1 cup/250 mL	163 mg
Lasagna – homemade	1 cup/250 mL	286 mg
Soup made with milk	1 cup/250 mL	189 mg

Adapted from Health Canada: Canadian Nutrient File, 1991.



Clinical Signs of Fractures or Osteoporosis

1. Height loss > 3 cm (Sn 92%)
2. Weight < 51 kg
3. Kyphosis (Sp 92%)
4. Tooth count < 20 (Sp 92%)
5. Grip strength
6. Armspan-height difference > 5 cm (Sp 76%)
7. Wall-occiput distance > 0 cm (Sp 87%)
8. Rib-pelvis distance ≤ 2 finger breadth (Sn 88%)

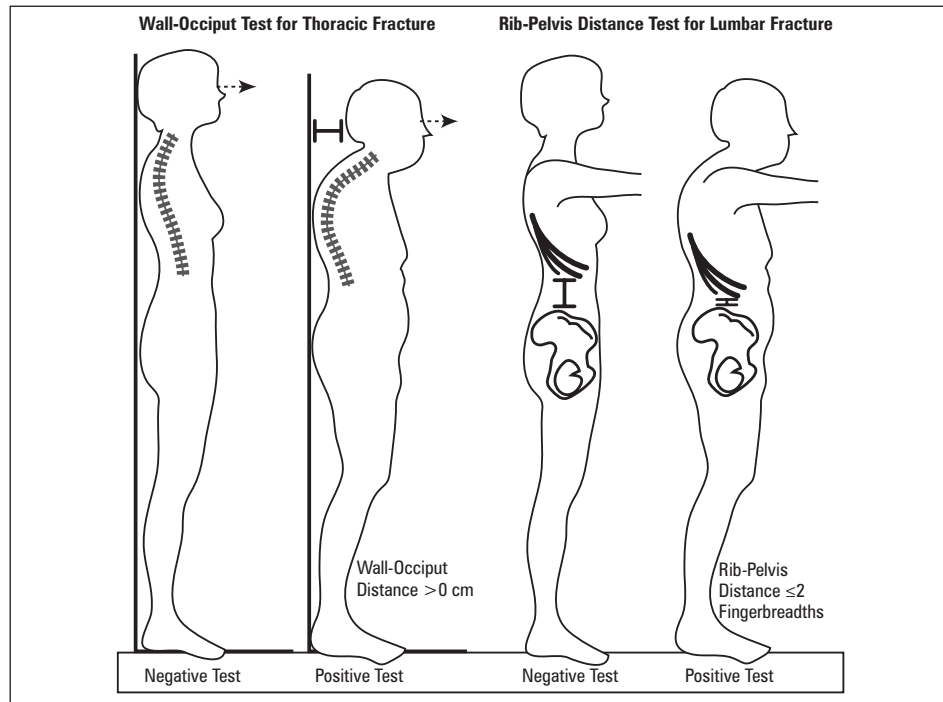


Figure 17. Physical Examination Test

Clinical Features

- commonly asymptomatic
- collapsed vertebrae → height loss
- fractures
 - commonly occur in hip, vertebrae, humerus, and wrist
 - fragility fractures: fracture with fall from standing height
 - Dowager's hump = collapse fracture of vertebral bodies in mid-dorsal region
 - x-ray: vertebral compression and crush fractures, wedge fractures, "codfishing" sign (weakening of subchondral plates and expansion of intervertebral discs)
- pain, especially backache, associated with fractures

Investigations

- usually normal serum Ca, PO₄, alkaline phosphatase
- also measure 25(OH)-vit D, TSH, serum and urine protein electrophoresis, celiac workup and 24 hr urinary Ca excretion to r/o secondary causes
- densitometry
 - dual-energy x-ray absorptiometry (DEXA) – gold standard in diagnosis of osteoporosis, (quantitative CT, ultrasonography)
 - lumbar spine and femur
 - compared with gender and ethnicity-matched controls
 - osteopenia: bone mineral density 1.5-2.5 SD below mean
 - osteoporosis: >2.5 SD below mean

Screening: Who should we screen?

- DEXA for:
 - women and men ≥ 65 yr
 - postmenopausal women < 65 with risk factors
 - premenopausal women or men with fragility fractures of secondary causes
 - YES on risk assessment tools: SCORE questionnaire ≥ 6 or ORAI ≥ 9
 - ♦ if NO reassess in 1-2 years

Treatment of Osteoporosis

Table 36. Treatment of Osteoporosis in Women and Men

	Women	Men
Whom to Treat?	Postmenopausal: • T-score < -2.5 with no risk factors • T-score < -1.5 with ≥ 1 risk factors • Any spine or hip #	• > 65 with T-score < -2.5 at any site • > 50 with a fragility/vertebral compression #, OR any age with glucocorticoid therapy ≥ 3 mth OR any age with hypogonadism, AND T-score < -1.5
Lifestyle	Diet: Elemental calcium 1000-1500 mg/day; Vit D 800 IU/day Exercise: 3x30 min weight-bearing exercises/wk Cessation of smoking, reduce caffeine intake Stop/avoid osteoporosis-inducing medications	
Drug Therapy Bisphosphonate: Inhibitors of osteoclast binding	Alendronate, strontium, ranelate, risedronate, zoledronate, etidronate, pamidronate	
SERM (selective estrogen-receptor modulator): agonistic effect on bone but antagonistic effect on uterus and breast	Raloxifene: • +ve: prevents osteoporotic # (Grade A to B evidence), improves lipid profile, decreased breast ca risk • -ve: increased risk of DVT/PE, stroke mortality, hot flashes, leg cramps	
Parathyroid Hormone	YES fragility #: 18-24 mo duration	
Calcitonin (2nd line): osteoclast receptor binding	YES fragility #: Calcitonin 200 IU nasally OD with Calcitriol 0.25 µg BID	
HRT: combined estrogen + progesterone	For most women, risks > benefits • Combined estrogen/progestin prevents hip, vertebral, total # • Increased risks of breast ca and cardiovascular events	



Bisphosphonates are considered first-line treatment in women with established osteoporosis.

Alendronate for the Primary and Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women
Cochrane Database Syst Rev 2008;(1):CD001155

Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women
Cochrane Database Syst Rev. 2008;(1):CD003376.

Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women
Cochrane Database Syst Rev. 2008;(1):CD004523.

Purpose: To assess the efficacy of three bisphosphonates in the primary and secondary prevention of osteoporotic fractures in postmenopausal women.
Study Selection: Women receiving at least one year of bisphosphonates for postmenopausal osteoporosis were compared to those receiving placebo or concurrent calcium/vitamin D or both. The outcome was fracture incidence.
Results: Levels of evidence: <http://www.cochraneskt.org/review/writing/>
%RRR and %ARR for 5 year fracture incidence reduction.

	Alendronate (10 mg/d)
1° Prevention - Vertebral	45% RRR, 2% ARR (Gold)
1° Prevention - Hip	Not significant
1° Prevention - Wrist	Not significant
2° Prevention - Vertebral	45% RRR, 6% ARR (Gold)
2° Prevention - Hip	53% RRR, 1% ARR (Gold)
2° Prevention - Wrist	50% RRR, 2% ARR (Gold)
	Etidronate (400 mg/d)
1° Prevention - Vertebral	Not significant
1° Prevention - Hip	Not significant
1° Prevention - Wrist	Not significant
2° Prevention - Vertebral	47% RRR, 5% ARR (Silver)
2° Prevention - Hip	No benefit
2° Prevention - Wrist	No benefit
	Risedronate (5 mg/d)
1° Prevention - Vertebral	Not significant
1° Prevention - Hip	Not significant
1° Prevention - Wrist	Not significant
2° Prevention - Vertebral	39% RRR, 5% ARR (Gold)
2° Prevention - Hip	26% RRR, 1% ARR (Silver)
2° Prevention - Wrist	Not significant

Osteomalacia and Rickets

- **rickets** – osteopenia with disordered calcification leading to higher proportion of osteoid (unmineralized) tissue prior to epiphyseal closure (in childhood)
- **osteomalacia** – osteopenia with disordered calcification leading to higher proportion of osteoid (unmineralized) tissue after epiphyseal closure (in adulthood)

Etiology and Pathophysiology

Vitamin D Deficiency

- leads to secondary hyperparathyroidism and hypophosphatemia
- deficient uptake or absorption
 - nutritional deficiency
 - malabsorption: post-gastrectomy, small bowel disease (e.g. Celiac sprue), pancreatic insufficiency
- defective 25-hydroxylation
 - liver disease
 - anticonvulsant therapy
- loss of vitamin D binding protein
 - nephrotic syndrome
- defective 1-alpha-25 hydroxylation
 - hypoparathyroidism
 - renal failure

Mineralization Defect

- abnormal matrix
 - osteogenesis imperfecta
 - fibrogenesis imperfecta
 - axial osteomalacia
- enzyme deficiency
 - hypophosphatasia (inadequate ALP bioactivity)
- presence of calcification inhibitors
 - bisphosphonates, aluminum, high dose fluoride, anticonvulsants

Phosphate Deficiency

- decreased intake
 - antacids
- impaired renal reabsorption
 - primary defect: Wilson's syndrome, Fanconi syndrome, multiple myeloma
 - secondary defect: primary hyperparathyroidism, oncogenic osteomalacia



Factors Necessary for Mineralization

- Quantitatively and qualitatively normal osteoid formation
- Normal concentration of calcium and phosphate in ECF
- Adequate bioactivity of ALP
- Normal pH at site of calcification
- Absence of inhibitors of calcification

Table 37. Clinical Presentations of Rickets and Osteomalacia

Rickets	Osteomalacia
<ul style="list-style-type: none"> Skeletal pain and deformities, bow legged Fracture susceptibility Weakness and hypotonia Disturbed growth Ricketic rosary (prominent costochondral junctions) Harrison's groove (indentation of lower ribs) Hypocalcemia 	<ul style="list-style-type: none"> Not as dramatic Diffuse skeletal pain Bone tenderness Fractures Gait disturbances (waddling) Proximal muscle weakness Hypotonia

Investigations

Table 38. Laboratory Findings in Osteomalacia and Rickets

Disorder	Serum Phosphate	Serum Calcium	Serum ALP	Other Features
Vit D deficiency	Decreased	Decreased to normal	Increased	Decreased calcitriol
Hypophosphatemia	Decreased	Normal	Decreased to normal	
Proximal RTA	Decreased	Normal	Normal	Associated with hyperchloremic metabolic acidosis
Conditions associated with abnormal matrix formation	Normal	Normal	Normal	

- radiologic findings
 - pseudofractures, fissures, narrow radiolucent lines – thought to be healed stress fractures or the result of erosion by arterial pulsation
 - loss of radiologic distinctness of vertebral body trabecula, concavity of the vertebral bodies
 - changes due to secondary hyperparathyroidism: subperiosteal resorption of the phalanges, bone cysts, resorption of the distal ends of long bones
 - others: bowing of tibia, coxa profundus hip deformity
- bone biopsy
 - usually not necessary but considered the gold standard for diagnosis

Treatment

- depends on the underlying cause
- vitamin D supplementation
- PO₄ supplements if low serum PO₄ is present
- Ca supplements for isolated calcium deficiency
- bicarbonate if chronic acidosis

Renal Osteodystrophy

- represents a mixture of four types of bone disease
 - low turn-over osteomalacia – from acidosis and retention of toxic metabolites
 - osteoporosis – metabolic acidosis dissolution of bone buffers
 - osteitis fibrosa cystica – from increased PTH
 - osteosclerosis – from increased PTH
- metastatic calcification secondary to hyperphosphatemia may occur

Pathophysiology

- metabolic bone disease secondary to chronic renal failure
- combination of hyperphosphatemia (inhibits 1,25(OH)₂-vit D synthesis) and loss of renal mass (reduced 1-alpha-hydroxylase)

Clinical Features

- soft tissue calcifications → necrotic skin lesions if vessels involved
- osteodystrophy → generalized bone pain and fractures
- pruritus
- neuromuscular irritability and tetany may occur
- radiologic features of osteitis fibrosa cystica, osteomalacia, osteosclerosis, osteoporosis

Treatment

- prevention
 - maintenance of normal serum Ca and PO₄ by restricting PO₄ intake to 1 g OD
 - Ca supplements
 - PO₄ binding agents
 - prophylactic use of vitamin D with close monitoring to avoid hypercalcemia and metastatic calcification

Paget's Disease of Bone

Definition

- a metabolic disease characterized by excessive bone destruction and repair

Epidemiology

- a common disease: 5% of the population, 10% of population >80 years old

Etiology

- postulated to be related to a slow progressing viral infection of osteoclasts, possibly paramyxovirus
- strong familial incidence

Pathophysiology

- initiated by increased osteoclastic activity leading to increased bone resorption; osteoblastic activity increases in response to produce new bone that is structurally abnormal and fragile

Differential Diagnosis

- primary bone lesions
 - osteogenic sarcoma
 - multiple myeloma
 - fibrous dysplasia
- secondary bone lesions
 - osteitis fibrosa cystica
 - metastases

Clinical Features

- usually asymptomatic (routine x-ray finding or elevated alkaline phosphatase)
- severe bone pain (e.g. pelvis, femur, tibia) is often the presenting complaint
- skeletal deformities – bowed tibias, kyphosis, frequent fractures
- skull involvement – headaches, increased hat size, deafness
- increased warmth over involved bones due to increased vascularity

Investigations

- laboratory
 - serum alkaline phosphatase is usually very high (unless burnt out)
 - normal or increased serum Ca
 - normal serum PO_4
 - increased urinary hydroxyproline (indicates resorption)
- imaging
 - evaluate the extent of disease with bone scan
 - initial lesion may be destructive and radiolucent
 - involved bones are expanded with cortical thickening and denser than normal
 - multiple fissure fractures in long bones

Complications

- local
 - fractures
 - osteoarthritis
 - cranial nerve compression and palsies, e.g. deafness
 - spinal cord compression
 - osteosarcoma/sarcomatous change
 - ♦ 1 to 3%
 - ♦ indicated by marked bone pain, new lytic lesions and sudden increased alkaline phosphatase
- systemic
 - hypercalcemia and nephrolithiasis
 - high output congestive heart failure due to increased vascularity

Treatment

- symptomatic therapy
- treat if ALP >3x normal
- bisphosphonates, e.g. alendronate 40 mg PO OD x 6 months OR risendronate 30 mg PO OD x 3 months OR zoledronic acid 5 mg IV per year
- calcitonin 50-100 U/day subcutaneous injection
- adequate calcium and vitamin D intake to prevent development of secondary hyperparathyroidism

Comparison of a Single Infusion of Zoledronic Acid with Risedronate for Paget's Disease

NEJM 2005; 353:898-908

Study: Two identical, randomized, double-blind, actively controlled trials (combined for analysis).

Patients: 357 men and women who were older than 30 years of age and had radiologically confirmed Paget's disease of bone. All but 4 patients had alkaline phosphatase levels that were more than twice the upper limit of normal.

Intervention: One 15-minute infusion of 5 mg of zoledronic acid with 60 days of oral risedronate (30 mg per day) with follow up at 6 months.

Primary Outcome: Rate of therapeutic response at six months, defined as a normalization of alkaline phosphatase levels or a reduction of at least 75 percent in the total alkaline phosphatase excess.

Results: At six months, 96.0 percent of patients receiving zoledronic acid had a therapeutic response (169 of 176), as compared with 74.3 percent of patients receiving risedronate (127 of 171, $P < 0.001$). Alkaline phosphatase levels normalized in 88.6 percent of patients in the zoledronic acid group and 57.9 percent of patients in the risedronate group ($P < 0.001$). Zoledronic acid was associated with a shorter median time to a first therapeutic response (64 vs. 89 days, $P < 0.001$). Higher response rates in the zoledronic acid group were consistent across all demographic, disease-severity, and treatment-history subgroups and with changes in other bone-turnover markers. The physical-component summary score of the Medical Outcomes Study 36-item Short-Form General Health Survey, a measure of the quality of life, increased significantly from baseline at both three and six months in the zoledronic acid group and differed significantly from those in the risedronate group at three months. Pain scores improved in both groups. During post-trial follow-up (median, 190 days), 21 of 82 patients in the risedronate group had a loss of therapeutic response, as compared with 1 of 113 patients in the zoledronic acid group ($P < 0.001$).

Conclusions: A single infusion of zoledronic acid produces more rapid, more complete, and more sustained responses in Paget's disease than does daily treatment with risedronate.



Male Reproductive Endocrinology

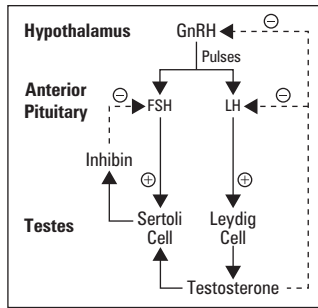


Figure 18. Hypothalmo-Pituitary-Gonadal Axis

Androgen Regulation

- both positive and negative feedback may occur by androgens directly or after conversion to estrogen
- testosterone (from the Leydig cell) primarily involved in negative feedback on LH, whereas inhibin (from the Sertoli cell) suppresses FSH secretion

Tests of Testicular Function

- testicular size (lower limit = 4 cm x 2.5 cm)
- LH, FSH, testosterone
- human chorionic gonadotropin (hCG) stimulation test
 - assesses ability of Leydig cell to respond to gonadotropin
- semen analysis
 - semen volume, sperm count, morphology and motility
- testicular biopsy
 - indicated in the context of normal FSH and azoospermia/oligospermia

Hypogonadism and Infertility

- see Urology, U34
- deficiency in gametogenesis or testosterone production

Etiology

- causes include primary (testicular failure) and secondary (hypothalamic-pituitary failure)
- primary hypogonadism is more common than secondary

Table 39. Classification and Features of Hypogonadism

	Hypergonadotropic Hypogonadism (Primary Hypogonadism)	Hypogonadotropic Hypogonadism (Secondary Hypogonadism)
Definition	Primary testicular failure ↑ LH and FSH, ↑ FSH:LH ratio ↓ testosterone and sperm count	Hypothalamic-pituitary axis failure ↓ LH + FSH ↓ testosterone and sperm count
Etiology	Congenital: <ul style="list-style-type: none"> • Chromosomal defects (Klinefelter's, Noonan) • Cryptorchidism • Male pseudohermaphroditism • Bilateral anorchia (vanishing testicle syndrome) • Myotonic dystrophy • Mutation of FSH or LH receptor gene • Varicocele • Disorders of androgen synthesis Germ cell defects <ul style="list-style-type: none"> • Sertoli cell only syndrome • Leydig cell aplasia/failure Infection/ Inflammation <ul style="list-style-type: none"> • Orchitis – TB, lymphoma, mumps, leprosy • Genital tract infection Physical factors <ul style="list-style-type: none"> • Trauma, heat, irradiation, testicular torsion Drugs <ul style="list-style-type: none"> • Marijuana, alcohol, chemotherapy, ketoconazole, glucocorticoid Autoimmune	Congenital <ul style="list-style-type: none"> • Kallman's syndrome • Prader-Willi syndrome • Abnormal subunit of LH or FSH Infection <ul style="list-style-type: none"> • Tuberculosis, meningitis Endocrine <ul style="list-style-type: none"> • Adrenal androgen excess • Cushing's syndrome • Hypo or hyperthyroidism • Hypothalamic-pituitary disease (tumour, hyperprolactinemia, hypopituitarism) Drugs <ul style="list-style-type: none"> • Alcohol, marijuana, spironolactone, ketoconazole, GnRH agonists, androgen/estrogen/progestin use, chronic narcotic use Chronic illness <ul style="list-style-type: none"> • Cirrhosis, chronic renal failure, AIDS • Sarcoidosis, Langerhan's cell histiocytosis, hemochromatosis Critical illness <ul style="list-style-type: none"> • Surgery, MI, head trauma Idiopathic
Diagnosis	Sperm count LH, FSH, testosterone hCG stimulation Testicular size and consistency (soft/firm) Karyotype	Sperm count LH, FSH, testosterone Prolactin levels MRI of hypothalamic-pituitary region



Two Distinct Features of Primary Hypogonadism

1. The decrease in sperm count is affected to a greater extent than the decrease in serum testosterone level
2. Likely to be associated with gynecomastia



Two Features of Secondary Hypogonadism

1. Associated with an equivalent decrease in sperm count and serum testosterone
2. Less likely to be associated with gynecomastia

Treatment

- testosterone replacement (improve libido, muscle mass, strength, hair growth)
 - IM injection, transdermal testosterone patch/gel
 - side effects: acne, fluid retention, erythrocytosis, sleep apnea (rare)
 - contraindicated if history of prostate cancer
- GnRH agonist to restore fertility
 - administered SC in pulsatile fashion using an external pump
- surgery – only if testicular tissues are not functioning

Causes of Male Infertility

1. primary hypogonadism
2. secondary hypogonadism
3. other causes:
 - autoimmune disorders – sperm antibody
 - anatomy – hypospadias, retrograde ejaculation
 - sexual dysfunction – erectile dysfunction, premature ejaculation, infrequent coitus
 - obstruction – vasal occlusion, vasal aplasia, vasectomy, seminal vesicle disease

DEFECTS IN ANDROGEN ACTION**Etiology**

- complete androgen insensitivity (testicular feminization)
- incomplete androgen insensitivity
 - 5-alpha-reductase deficiency
 - mixed gonadal dysgenesis
 - defects in testosterone synthesis
- infertile male syndrome
- undervirilized fertile male syndrome

Clinical Features

- depends on age of onset

Table 40. Effects of Testosterone Deficiency

First trimester in utero	Incomplete virilization of external genitalia (ambiguous genitalia) Incomplete development of Wolffian ducts to form male internal genitalia (male pseudohermaphroditism)
Third trimester in utero	Micropenis Cryptorchidism (failure of normal testicular descent)
Prepuberty	Incomplete pubertal maturation (high pitch voice, sparse pubic + axillary hair, absence of facial hair) Eunuchoidal body habitus (greater growth of extremity long bones relative to axial bones) Poor muscle development, reduced peak bone mass
Postpuberty	Decrease in energy, mood, and libido Fine wrinkles in corners of mouth and eyes Decrease in sexual hair, hematocrit, muscle mass, strength and bone mineral density

Adapted from UpToDate, 2010 + Cecil's Essentials of Medicine

Treatment

- appropriate gender assignment in the newborn
- hormone replacement or supplementation
- psychological support
- gonadectomy for cryptorchidism (due to increased risk for testicular cancer)
- reduction mammoplasty for gynecomastia

**Approach to Male Infertility****History**

- Partner status re: infertility
- Length of time for attempt to conceive
- Prior successes with other partners
- Ejaculation problems
- Frequency of intercourse
- Prev Surg, Med Hx, STD Hx
- Hx orchitis? Cryptorchidism?
- Hx toxic exposure?
- Medications
- Alcohol and illicit drug use
- Heat exposure: bath, sauna, whirlpool
- Smoking

P/E

- Testicular size and consistency
- Varicocele?
- Pituitary disease?
- Thyroid disease?

Investigations

- Semen analysis x 2 (sperm count, morphology, motility)
- Scrotal/Testicular U/S (look for varicocele)
- Bloodwork: LH, FSH, Testosterone, Prolactin, TFT's, DNA fragmentation of sperm, Karyotype, Y chromosome deletion

Treatment

- No specific therapy for majority of cases
- Treat specific causes
- Consider: intrauterine insemination, IVF, therapeutic donor insemination, testicular aspiration of sperm, adoption

Erectile Dysfunction

- see Urology, U30

**Epidemiology of Gynecomastia****Occurrence of Gynecomastia****3 peaks % affected**

Infancy	60-90
Puberty	4-69
Ages 50-80	24-65

**Causes of Gynecomastia****DOC TECH**

Drugs

Other

Congenital

Tumour

Endocrine

CHronic disease

Gynecomastia

Definition

- true gynecomastia refers to benign proliferation of the glandular component of the male breast, resulting in the formation of a concentric, rubbery, firm mass extending from the nipple(s)
- pseudogynecomastia or lipomastia refers to enlargement of soft adipose tissue, especially seen in obese individuals and does not warrant further evaluation

Etiology**Physiologic**

- puberty
- elderly (involutional)
- neonatal (maternal hormone)

Pathologic

- endocrinopathies – primary or secondary hypogonadism, hyperthyroidism, extreme hyperprolactinemia, adrenal disease
- tumours – pituitary, adrenal, testicular, breast
- chronic diseases – liver, renal, malnutrition (with refeeding)
- drugs – estrogens and estrogen agonists, spironolactone, ketoconazole, cimetidine, digoxin, chemotherapy, marijuana, alcohol
- congenital/genetic – Klinefelter's syndrome, androgen insensitivity
- other – idiopathic, familial

Pathophysiology

- decreased androgen production + increased estrogen production
- increased availability of estrogen precursors for peripheral conversion to estrogen
- androgen receptor blockage + binding of androgen to sex hormone binding globulin (SHBG)

History

- recent change in breast characteristics
- history of trauma to testicles
- history of mumps
- alcohol and/or drug use
- family history
- sexual dysfunction

Physical Exam

- signs of feminization
- breast
 - must differentiate from breast cancer (unilateral, eccentric, hard/firm mass, fixed to underlying tissue) with possible skin changes (dimpling, retraction) or nipple changes (discharge, crusting)
 - gynecomastia in contrast occurs concentrically around nipple, and is not fixed to underlying tissue
- genito-urinary exam
- stigmata of liver or thyroid disease

Investigations

- laboratory – serum TSH, PRL, LH, FSH, free testosterone, estradiol, LFTs, creatinine, hCG (if hCG is elevated, need to locate the primary tumour)
- CXR and CT of chest/abdomen/pelvis (to locate neoplasm)
- testicular U/S to rule out testicular mass
- MRI of hypothalamic-pituitary region

Treatment

- medical
 - correct the underlying disorder, discontinue responsible drug
 - androgens for hypogonadism
 - anti-estrogens – tamoxifen, clomiphene
- surgical
 - usually required if have macromastia; gynecomastia present for >1 year (fibrosis is unresponsive to medication); or failed medical treatment and for cosmetic purposes

Common Medications

Diabetes Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects	Comments	
Biguanide	<ul style="list-style-type: none">• Sensitizes peripheral tissues to insulin → increases glucose uptake• Decreases hepatic glucose production	metformin	Glucophage® Glumetza®		500 mg OD titrated to 1000 mg bid maximum	<ul style="list-style-type: none">• Useful in obese Type 2 DM• Improves both fasting and postprandial hyperglycemia• Also ↓ TG	ABSOLUTE: <ul style="list-style-type: none">• Moderate to severe liver dysfunction• Moderate renal dysfunction• Cardiac dysfunction	<ul style="list-style-type: none">• GI upset (abdo discomfort, bloating, diarrhea)• Lactic acidosis• Anorexia	↓ HbA1C 1.0-1.5%	
Insulin secretagogue	<ul style="list-style-type: none">• Stimulates insulin release from beta cells by causing K channel closure → depolarization → Ca mediated insulin release• Use in nonobese Type 2 DM									
		sulfonylureas: glyburide	Diabeta® Euglucon®	Micronase® Glynase Prestab®	2.5-5.0 mg/day titrated to >5 mg bid Max: 20 mg/day		ABSOLUTE: <ul style="list-style-type: none">• Moderate to severe liver dysfunction RELATIVE: <ul style="list-style-type: none">• Adjust dose in patients with severe kidney dysfunction (and avoid glyburide in these patients)• Avoid glyburide in the elderly INTERACTIONS: <ul style="list-style-type: none">Do not combine with a non-sulfonylurea or preprandial insulin	<ul style="list-style-type: none">• Hypoglycemia• Weight gain	↓ HbA1C 1.0-1.5%	
		glizalide	Diamicon® Diamicon® MR		40-160 mg bid 30-120 mg OD					
		glimepiride	Amaryl®		1-8 mg OD					
Insulin sensitizers (thiazolidinedione)	<ul style="list-style-type: none">• Sensitizes peripheral tissues to insulin → increases glucose uptake• Decreases FFA release from adipose• Binds to nuclear receptor									
		non-sulfonylureas: repaglinide	GlucoNorm®		0.5-4 mg tid	<ul style="list-style-type: none">• Short t_{1/2} of 1 hour causes brief but rapid ↑ in insulin, therefore effective for post prandial control	ABSOLUTE: <ul style="list-style-type: none">• Severe liver dysfunction• Severe renal dysfunction INTERACTIONS: <ul style="list-style-type: none">Do not combine with a non-sulfonylurea or preprandial insulin	<ul style="list-style-type: none">• Hypoglycemia• Weight gain	↓ HbA1C 1.0-1.5% for repaglinide and 0.5-1.0% for nateglinide	
		nateglinide	Starlix®		60-120 mg tid					
α-glucosidase inhibitor	<ul style="list-style-type: none">• Sensitizes peripheral tissues to insulin → increases glucose uptake• Decreases FFA release from adipose• Binds to nuclear receptor									
		rosiglitazone	Avandia®		2-8 mg OD		ABSOLUTE: <ul style="list-style-type: none">• Severe liver dysfunction• NYHA > class II CHF INTERACTIONS: <ul style="list-style-type: none">Do not combine with insulin	<ul style="list-style-type: none">• Peripheral edema• Pulmonary edema• CHF• Anemia• Weight gain• Fractures	↓ HbA1C 1.0-1.5%	
α-glucosidase inhibitor	<ul style="list-style-type: none">• Sensitizes peripheral tissues to insulin → increases glucose uptake• Decreases FFA release from adipose• Binds to nuclear receptor									
		pioglitazone	Actos®		15-45 mg OD					
α-glucosidase inhibitor	<ul style="list-style-type: none">• ↓ carbohydrate GI absorption by inhibiting brush border α-glucosidase									
		acarbose	Glucobay®		25 mg OD titrated to 100 mg tid	<ul style="list-style-type: none">• ↓ postprandial hyperglycemia	ABSOLUTE: <ul style="list-style-type: none">• Inflammatory bowel disease• Severe liver dysfunction	<ul style="list-style-type: none">• Flatulence• Abdominal cramps• Diarrhea	↓ HbA1C 0.5-1.0%	
Dipeptidyl peptidase-IV (DPP-IV) inhibitor	<ul style="list-style-type: none">• Inhibits degradation of endogenous antihyperglycemic incretin hormones• Incretin hormones stimulate insulin secretion, inhibit glucagon release, and delay gastric emptying									
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For insulin formulations, please refer to E9

Dyslipidemia Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
HMG CoA reductase inhibitor	• Inhibits cholesterol biosynthesis, ↓ LDL synthesis, ↑ LDL clearance, modest ↑ HDL, limited ↓ VLDL	atorvastatin fluvastatin lovastatin pravastatin rosuvastatin simvastatin	Lipitor® Lescol® Mevacor® Pravachol® Crestor® Zocor®		10-80 mg/day 20-80 mg/day 20-80 mg/day 10-40 mg/day 5-40 mg/day 10-80 mg/day	• 1 st line monotherapy • Used for ↑ LDL, ↑ TG	• Active liver disease • Persistent ↑ in AST, ALT	• GI symptoms • Rash, pruritus • ↑ liver enzymes • Myositis (↑ risk if combined with fibrates) • Rhabdomyolysis (dose >80 mg)
Fibrates	• Upregulate lipoprotein lipase + Apo A1, ↓ VLDL, ↓ TG, modest ↓ LDL, modest ↑ HDL	bezafibrate fenofibrate gemfibrozil	Bezalip® Lipidil® Lopid®		400 mg/day 48-200 mg/day 600-1200 mg/day	• Used for ↑ TG, hyperchylomicronemia	• Hepatic disease • Renal disease	• GI upset • ↑ risk of gallstone formation • ↑ risk of rhabdomyolysis when combined with statins
Niacin	• Inhibits secretion of hepatic VLDL via lipoprotein lipase (LPL) pathway → decreased VLDL and LDL; decreased clearance of HDL	nicotinic acid	Niaspan® generic niacin	Niacor®	0.5-2 g/day 1-3 g/day	• Used for ↑ LDL, ↑ VLDL	• Hypersensitivity • Hepatic dysfunction • Active PUD • Overt DM • Hyperuricemia	• Generalized flushing • Abnormal liver enzymes • Pruritus • IGT • Severe hypertension
Bile acid sequestrants	• Resins that bind bile acids in intestinal lumen and prevent absorption thereby ↓ LDL	cholestyramine	Questran® Prevalite®		2-24 g/day	• Used for ↑ LDL • Use as adjunct with statins or fibrates	• Complete biliary obstruction • Pregnancy, lactation • TG > 300 mg/dL • GI motility disorder	• Constipation • Nausea • Flatulence • Bloating
Cholesterol absorption inhibitors	• Inhibits cholesterol absorption at the small intestine brush border	colesevelam	Colestid® Ezetrol®	Zetia®	5-30 g/day 10 mg/day	• Used for ↑ LDL, Apo B	• Hypersensitivity • Hepatic dysfunction • Don't combine with fibrates or bile acid resins	• Fatigue • Pharyngitis • Sinusitis • Abdominal pain • Diarrhea • Arthralgia

Thyroid Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Antithyroid Agent	• Decreases thyroid hormone production by inhibiting iodine and peroxidase from interacting with thyroglobulin to form T ₄ and T ₃ • Also interferes with conversion of T ₄ to T ₃	propylthiouracil (PTU)	Propyl-Thyracil® Tapazole®		Start 100 mg PO tid, then adjust accordingly Thyroid storm: start 200-300 PO qid, then adjust accordingly	• Hyperthyroidism	• Hypersensitivity • Relative: renal failure, liver disease	• Nausea, vomiting • Rash • Drug-induced hepatitis • Agranulocytosis
		methimazole (MMI)			Start 5-20 mg PO OD, then adjust accordingly		• Pregnancy, lactation	• Hepatitis
Thyroid hormone	• Synthetic form of thyroxine (T ₄)	levothyroxine l-thyroxine	Synthroid® Levothroid® Unithroid®	Levoxyl®	0.05-2.0 mg/day, in elderly patients start at 0.025 mg/day	• Hypothyroidism	• Recent MI, thyrotoxicosis	• Symptoms of hyperthyroidism • Tachycardia • Angina • Weight loss • Hyperthermia • Diarrhea • Insomnia • Tremors • Muscle weakness

Metabolic Bone Disease Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Bisphosphonates	<ul style="list-style-type: none"> Inhibits osteoclast-mediated bone resorption 	alendronate	Fosamax®		5-10 mg OD 70 mg once weekly 40 mg OD for 6 months	<ul style="list-style-type: none"> Prevention of postmenopausal osteoporosis Treatment of osteoporosis Glucocorticoid-induced osteoporosis Paget's disease 	<ul style="list-style-type: none"> Esophageal stricture or achalasia (oral) Unable to stand or sit upright for >30 min (oral) Hypersensitivity Hypocalcemia Renal insufficiency 	<ul style="list-style-type: none"> GI MSK pain Headache Osteonecrosis of the jaw
		risatronate	Actonel®		5 mg OD 35 mg once weekly 150 mg once monthly 30 mg OD for 2 months	<ul style="list-style-type: none"> Treatment and prevention of postmenopausal osteoporosis Treatment and prevention of glucocorticoid-induced osteoporosis Paget's disease 		
		etidronate	Didronel®		5-10 mg/kg OD x 6 months	<ul style="list-style-type: none"> Osteoporosis Symptomatic Paget's disease Prevention and treatment of heterotopic ossification after total hip replacement or spinal cord injury 		
		ibandronate	Boniva®		2.5 mg OD or 150 mg once monthly	<ul style="list-style-type: none"> Treatment and prevention of postmenopausal osteoporosis (US only) 		
		panidronate	Aredia®		IV	<ul style="list-style-type: none"> Hypercalcemia of malignancy Paget's disease Osteolytic bone metastases of breast cancer Osteolytic lesions of multiple myeloma 		
		zoledronate	Zometa® Aclasta®		5 mg IV once yearly IV	<ul style="list-style-type: none"> Treatment of osteoporosis Hypercalcemia of malignancy Treatment and prevention of skeletal complications related to cancer 		
Selective Estrogen Receptor Modulators	<ul style="list-style-type: none"> Decreases resorption of bone through binding to estrogen receptors 	raloxifene	Evista®		60 mg OD	<ul style="list-style-type: none"> Treatment and prevention of postmenopausal osteoporosis (2nd line) 	<ul style="list-style-type: none"> Lactation Pregnancy Active or past history of DVT, PE or retinal vein thrombosis 	<ul style="list-style-type: none"> Hot flashes Leg cramps Increased risk of fatal stroke, venous thromboembolism
Calcitonin	<ul style="list-style-type: none"> Inhibits osteoclast-mediated bone resorption 	salcatonin	Miacalcin®		One spray (200 IU) per day, alternating nostrils	<ul style="list-style-type: none"> Treatment of postmenopausal osteoporosis, greater than 5 years postmenopause 	<ul style="list-style-type: none"> Clinical allergy to calcitonin-salmon 	<ul style="list-style-type: none"> Rhinitis Epistaxis Sinusitis Nasal dryness
PTH	<ul style="list-style-type: none"> Stimulates new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity 	teriparatide	Forteo®		20 µg SC OD X 18-24 months	<ul style="list-style-type: none"> Treatment of postmenopausal women with osteoporosis who are at high risk for fracture Treatment of men with primary or hypogonadal osteoporosis who are at high risk for fracture 	<ul style="list-style-type: none"> Paget's disease Prior external beam or implant radiation therapy involving the skeleton Bone metastases Metabolic bone diseases other than osteoporosis 	<ul style="list-style-type: none"> Orthostatic hypotension Hypercalcemia Dizziness Leg cramps

Metabolic Bone Disease Medications (continued)

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Calcium	• Inhibits PTH secretion				1500 mg/day (including diet) Divide in 3 doses	• Osteopenia • Osteoporosis • Prevention of metabolic bone disease	• Caution with renal stones	• Vomiting • Constipation • Dry mouth
Vitamin D	• Regulation of calcium and phosphate homeostasis	cholecalciferol (vitamin D3)			800 IU/day	• Osteopenia • Osteoporosis • Prevention of metabolic bone disease	• Caution in patients on digoxin (risk of hypercalcemia may precipitate arrhythmia)	• Hypercalcemia • Headache • Nausea, vomiting • Constipation
		ergocalciferol (vitamin D2)	Osteoforte® Deltalin®		50000 IU	• Osteoporosis in patients with liver dysfunction, refractory rickets, hypoparathyroidism	• Hypercalcemia • Malabsorption syndrome • Decreased renal function	
		calcitriol (1,25(OH) ₂ -D)	Rocaltrol® Calcijex®		Start 0.25 µg/day Titrate up by 0.25 µg/day at 4-8 week intervals to 0.5-1 µg/day	• Hypocalcemia and osteodystrophy in patients with chronic renal failure on dialysis	• Hypercalcemia • Vitamin D toxicity	
					Start 0.25 µg/day Titrate up by 0.25 µg/day at 2-4 week intervals to 0.5-2 µg/day	• Hypoparathyroidism		

Adrenal Medications

Drug Class	Mineralocorticoid Activity	Generic Drug Name	Potency (relative to Cortisol)	Equivalent Dose (mg)	Duration of Action (t 1/2 in hours)	Dosing	Comments
Hydrocortisone	Yes	Cortef Solu-Cortef	1.0	20	8	Adrenal Crisis: 100 mg IV bolus, then 100 mg q 8 hr (continuous infusion x 24-48 hr) PO once stable (50 mg q 8hr x 48 hrs, then taper over 14 d) Chronic AI: 20-30 mg PO OD (2/3 AM, 1/3 PM)	• In high doses, mineralocorticoid side effects may emerge salt + water retention, ECF volume expansion, HTN, low K metabolic alkalosis
Cortisone acetate	Yes	Cortone Acetate	0.8	25	oral = 8 IM = 18 +	Adrenal Crisis: 25-300 mg/d PO/IM divided q12-24 hr Chronic AI: 25-35 mg/d	• Pro-drug which is converted to active form as hydrocortisone • High doses can result in mineralocorticoid side effects (see above)
Prednisone	No	Deltasone Liquid Pred	3.5	6	16-36	Adrenal Crisis: 5-60 mg/d PO qd or divided BID/QID	• Pro-drug which is converted to active form as prednisolone
Dexamethasone	No	Decadron AK-Dex Dexone	30	0.7	36-54	Adrenal Crisis: 4 mg IV; repeat q2-6 hr if necessary	• Used for undiagnosed adrenal insufficiency (won't interfere with serum cortisol levels)

Landmark Endocrinology Trials

Trial	Reference	Results
DIABETES		
DCCT	<i>NEJM</i> 1993; 329:977-86	Intensive blood glucose control delayed the onset and reduced the progression of microvascular complications (retinopathy, nephropathy and neuropathy) in Type 1 DM
UKPDS	<i>Lancet</i> 1998; 352:837-53	Intensive blood glucose control reduces microvascular, but not macrovascular complications in Type 2 DM
EDIC	<i>NEJM</i> 2005; 353:2644-53	Compared with conventional therapy, intensive diabetes therapy (goal HbA1C <6.05%) has long-term beneficial effects on the risk of cardiovascular disease in patients with Type 1 DM
ACCORD	<i>NEJM</i> 2008; 358:2560-72	Compared with standard therapy, the use of intensive therapy to target normal HbA1c levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events
ADVANCE	<i>NEJM</i> 2008; 358:2545-59	Intensive glucose control that lowered the HbA1C value to 6.5% reduced the incidence of nephropathy but did not significantly reduce major macrovascular events, death from cardiovascular events, or death from any cause. Hypoglycemia was more common in the intensive control group
VADT	<i>NEJM</i> 2009; 360:1-11	In patients with longstanding poorly controlled Type 2 DM, intensive glucose control had no significant effect on the rates of major cardiovascular events, death, or microvascular complications. Adverse events, predominantly hypoglycemia, were more common in the intensive control group
BARI-2D	<i>NEJM</i> 2009; 360:2503-15	In patients with both Type 2 DM and coronary artery disease, no significant difference was found in the rates of death and major cardiovascular events in patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization and insulin
Steno-2	<i>NEJM</i> 2008; 358:580-91	In at-risk patients with Type 2 DM, intensive intervention with multiple drug combinations and behaviour modification had sustained significant beneficial effects with respect to vascular complications and mortality. Multifactorial intervention is critical in the management of Type 2 DM
NAVIGATOR	<i>NEJM</i> 2010; 362:1463-90	In patients with impaired glucose tolerance, nateglinide did not reduce progression to diabetes or risk of cardiovascular events, while valsartan only reduced progression to diabetes
LIPIDS		
4S	<i>Lancet</i> 1994; 344:1383-89	In patients with angina or previous MI and high total cholesterol, simvastatin reduced: all-cause mortality, fatal and nonfatal coronary events, and need for coronary artery bypass surgery or angioplasty
HPS	<i>Lancet</i> 2002; 360:7-22	In high-risk patients with various cholesterol values, simvastatin reduced all-cause mortality, coronary deaths and major vascular events
TNT	<i>NEJM</i> 2005; 352:1425-35	Lipid-lowering therapy with atorvastatin 80 mg/day in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/day
FIELD	<i>Lancet</i> 2005; 366:1849-61	In patients with Type 2 DM, not previously on statin therapy, fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. It did reduce non-fatal myocardial infarctions and revascularizations
Jupiter	<i>NEJM</i> 2008; 359:2195-207	Rosuvastatin significantly reduced the incidence of major cardiovascular events in patients with elevated high-sensitivity C-reactive protein levels and no hyperlipidemia

References

- Agus AZ. Etiology of hypercalcemia. Uptodate Online 2010; Version 10.2. www.uptodate.com
- Agus AZ. Overview of metabolic bone disease. Uptodate Online 2002; Version 10.2. www.uptodate.com
- American Diabetes Association. Management of dyslipidemia in adults with diabetes (Position Statement). *Diabetes Care* 2002; 25(S1):S74-77.
- Arnold A. Classification and pathogenesis of the multiple endocrine neoplasia syndromes. Uptodate Online 2002; Version 10.2. www.uptodate.com
- United Kingdom Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 1998; 352:837-53.
- Braunwald E, Fauci AS, Kasper DL, Hauser SL et al. *Diabetes Mellitus in Harrison's Principles of Internal Medicine Volume 2*. New York: The McGraw Hill Companies, 2001. pp 2109-2135.
- Burman KD. Overview of thyroiditis. Uptodate Online 2002; Version 10.2. www.uptodate.com
- Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Canadian Journal of Diabetes* 2008; 32(Supplement 1): S1-S201.
- Canadian Task Force on Preventive Health Care. Prevention of osteoporosis and osteoporotic fractures in post-menopausal women. *Canadian Medical Association Journal* 2004; 170(11):1665-1667.
- Cheng A, Fantus IG. Oral antihyperglycemic therapy for type 2 diabetes mellitus. *Canadian Medical Association Journal* 2005; 172(2): 213-226.
- Dayan CM. Interpretation of thyroid function tests. *Lancet* 2001; 357:619-624.
- Fodor JG, Frohlich JJ, Genest JGG, McPherson PR. Recommendations for the management and treatment of dyslipidemia. *Canadian Medical Association Journal* 2000; 162(10):1441-1447.
- Genest J, Frohlich JJ, Fodor JG, McPherson PR. Recommendations of the management of dyslipidemia and the prevention of cardiovascular disease: 2003 update. *Canadian Medical Association Journal* 2003; 169(9):O1-O10.
- Greenspan FS, Garber DG. *Basic and Clinical Endocrinology*. New York: Lange Medical Books/ McGraw Hill, 2001. pp 100-163, 201-272, 623-761.
- Hirsch IB, Paoow DS, Brunzell J. Inpatient management of adults with diabetes. *Diabetes Care* 1995; 18(6):870-878.
- Kitabachi AE, Umpierrez GE, Murphy MB, Barret EJ et al. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 2001; 24(1):131-152.
- Kronenberg HM, Larsen PR, Melmed S, Polonsky K. *Williams Textbook of Endocrinology Ninth Edition*. Philadelphia: W.B. Saunders Company, 1998.
- NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis and Therapy. Osteoporosis prevention, diagnosis, and therapy. *Journal of the American Medical Association* 2001; 285(6):785-795.
- Orth DN. Evaluation of the response to ACTH in adrenal insufficiency. Uptodate Online 2002; Version 10.2. www.uptodate.com
- Dawson-Hughes B, Gold DT, Rodbard HW, Bonner Jr FJ et al. *Physician's guide to prevention and treatment of osteoporosis*. Washington: National Osteoporosis Foundation, 2003.
- Rosen HN, Rosenblatt M. Overview of the management of osteoporosis in women. Uptodate Online 2002; Version 10.2. www.uptodate.com.
- Ross DS. Disorders that cause hypothyroidism. Uptodate Online 2002; Version 10.2. www.uptodate.com
- Ryan EA. Pregnancy in diabetes. *Medical Clinics of North America* 1998; 82(2):823-845.
- Collins R, Armitage J, Parish S, Sleight PR. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360: 7-22.
- The Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344:1383-1389.
- Tsui E, Barnie A, Ross S, Parkes R et al. Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. *Diabetes Care* 2001; 24(10):1722-1727.
- Young WF, Kaplan NM. Diagnosis and treatment of pheochromocytoma in adults. Uptodate Online 2002; Version 10.2. www.uptodate.com

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Rash	42		
Rhinorrhea	43		
Sexually Transmitted Infections (STIs)	43		
Sinusitis	45		
Sleep Disorders	45		

**Patient-Centred Clinical Method**

- Explore/define patient problems and decide on management together
- Consider both agendas and find common ground

**Agendas in Family Medicine****Doctor's Agenda**

History, physical, investigation, diagnosis, plan

Patient's Agenda**FIFE**

Feelings

Ideas

Function

Expectations

Four Principles of Family Medicine

College of Family Physicians of Canada Guidelines**1. The family physician is a skilled clinician**

- in diagnosing and managing diseases common to population served
- recognizes importance of early diagnosis of serious life-threatening illnesses

2. Family medicine is a community-based discipline

- provides information and access to community services
- responds/adapts to changing needs and circumstances of the community

3. The family physician is a resource to a defined practice population

- serves as a health resource
- advocates for public policy to promote health

4. The patient-physician relationship is central to the role of the family physician

- committed to the person, not just the disease
- promotes continuity of patient care

Periodic Health Examination (PHE)

- Canadian Task Force on Preventive Health Care established in 1976, first published in 1979, last updated in 2005
- mandate: to develop and disseminate clinical practice guidelines for primary and preventive care
- recommendations are based on systemic analysis of scientific evidence
 - most notable recommendation is the abolition of the annual physical exam; replaced by the PHE

Purpose of the PHE

- primary prevention: identify risk factors for common diseases; counsel patients to promote healthy behaviour
- secondary prevention: presymptomatic detection of disease to allow early treatment and to prevent disease progression
- update clinical data
- enhance patient-physician relationship

**Adult Periodic Health Exam**

Male and female evidence-based preventative care checklist forms are available online at www.cfpc.ca.

**Classification of Recommendations**

- A Good** evidence to recommend the clinical preventative action.
- B Fair** evidence to recommend the clinical preventative action.
- C** Existing evidence is **conflicting** and does not allow to make a recommendation for or against use of the clinical preventative action; however, other factors may influence decision-making.
- D Fair** evidence to recommend **against** the clinical preventative action.
- E Good** evidence to recommend **against** the clinical preventative action.
- I Insufficient** evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making.

Table 1. Periodic Health Exam

	General Population	Special Population
DISCUSSION	<ul style="list-style-type: none"> • Dental hygiene (community fluoridation, brushing, flossing) (A) • Noise control and hearing protection (A) • Smokers: counsel on smoking cessation, provide <ul style="list-style-type: none"> • Nicotine replacement therapy (A) • Referral to smoking cessation program (B) • Dietary advice on leafy green vegetables and fruits (B) • Seat belt use (B) • Injury prevention (bicycle helmets, smoke detectors) (B) • Moderate physical activity (B) • Avoid sun exposure and wear protective clothing (B) • Problem drinking screening and counselling (B) • Counselling to protect against STIs (B) • Nutritional counselling and dietary advice on fat and cholesterol (B) 	<p>Pediatrics: Home visits for high risk families (A) Inquiry into developmental milestones (B)</p> <p>Adolescents: Counsel on sexual activity and contraceptive methods (B) Counsel to prevent smoking initiation (B)</p> <p>Perimenopausal women: Counsel on osteoporosis Counsel on risks/benefits of hormone replacement therapy (B)</p> <p>Adults > 65: Follow-up on caregiver concern of cognitive impairment (A) Multidisciplinary post-fall assessment (A)</p>
PHYSICAL	<ul style="list-style-type: none"> • Clinical breast exam (women age 50-69) (A) • Blood pressure measurement (B) • BMI measurement in obese adults (B) 	<p>Pediatrics: Repeated examinations of hips, eyes and hearing (especially in first year of life) (A) Serial heights, weights and head circumference (B) Visual acuity testing after age 2 (B)</p> <p>Adults > 65: Visual acuity (Snellen sight chart) (B) Hearing impairment (inquiry, whispered voice test, audioscope) (B)</p> <p>First degree relative with melanoma: Full body skin exam (B)</p>

Table 1. Periodic Health Exam (continued)

General Population	Special Population
TESTS <ul style="list-style-type: none"> Multiphase screening with the Hemoccult test (adults age >50 q1-2yrs) (A) Sigmoidoscopy (adults >50) (frequency not established) (B) Bone mineral density: if at risk (1 major or 2 minor criteria) Fasting lipid profile (C): <ul style="list-style-type: none"> Women age >50 or post-menopausal; earlier if at risk Men age >40; earlier if at risk (optimal frequency unknown, at least q5yrs) Fasting blood glucose: age >40 q3yrs (or sooner and more frequently if risk factors present) Syphilis screen if at risk (D) Men: PSA testing screening guidelines not established (I) Women: Mammography (women age 50-69) q1-2yrs (A) Pap smear annually (women age 18-69 if ever sexually active, start after sexual debut); q3yrs after 2 normal results (more frequently if concerns) 	Pediatrics: Routine hemoglobin for high risk infants (B) Blood lead screening of high risk infants (B) Diabetics: Urine dipstick (A) Fundoscopy (B) TB high risk groups: Mantoux skin testing (A) STI high risk groups: Voluntary HIV antibody screening (A) Gonorrhea screening (A) Chlamydia screening in women (B) FAP: Sigmoidoscopy and genetic testing (B) HNPCC: Colonoscopy (B)
THERAPY <ul style="list-style-type: none"> Folic acid supplementation to women of child-bearing age (A) Varicella vaccine for children age 1-12 and susceptible adolescents/adults (A) Rubella vaccine for all non-pregnant women of child-bearing age (B) Pharmacologic treatment of hypertension with dBp >90 mmHg (adults age 21-64, elderly specific subgroups) (A) Tetanus vaccine: routine booster q10yrs if had 1^o series (A) Pertussis vaccine: routine booster of acellular vaccine once during adulthood (can be given as dTap) 	Pediatrics: Routine immunizations (A) Hepatitis B immunization (A) Influenza high risk groups: Outreach strategies for vaccination (A) annual immunization (B), now recommended for all TB high risk groups: INH prophylaxis for household contacts or skin test converters (B) INH prophylaxis for high risk sub-groups (B) Immunocompetent/age ≥65/COPD: Pneumococcal vaccine (A)

Classification of recommendation in brackets. See sidebar on FM2.
Reference: Canadian Task Force on Preventative Health Care, 2005.



When Ordering Fasting Bloodwork

- Results are valid only if obtained with ≥12 hours of fasting.
- Remember, "fasting" means no food, no drinks (except small quantities of water), no gum, no smoking.
- Prescription medications are okay unless otherwise specified.



Guidelines Advisory Committee (GAC) Recommendations for Breast Cancer Screening

For women aged 40-69 years, there is fair evidence to recommend that routine teaching of breast self-examination (BSE) be excluded from the PHE. Research shows fair evidence of no benefit to BSE and good evidence of harm.

Health Promotion and Counselling

- health promotion is the most effective preventative strategy
- 40-70% of productive life lost annually is preventable
- there are several effective ways to promote healthy behavioural change, such as discussions appropriate to a patient's present stage of change

Motivational Strategies for Behavioural Change

Table 2. Motivational Strategies for Behavioural Change

Patient's Stage of Change	Physician's Aim	Physician's Plan
Pre-contemplation	Encourage patient to consider the possibility of change Assess readiness for change Increase patient's awareness of the problem and its risks	Raise issue in a sensitive manner Offer (not impose) a neutral exchange of information to avoid resistance
Contemplation	Understand patient's ambivalence and encourage change Build confidence and gain commitment to change	Offer opportunity to discuss pros and cons of change, using reflective listening
Preparation	Explore options and choose course most appropriate to patient Identify high-risk situations and develop strategies to prevent relapse Continue to strengthen confidence and commitment	Offer realistic options for change and opportunity to discuss inevitable difficulties
Action	Help patients design rewards for success Develop strategies to prevent relapse Support and reinforce convictions towards long-term change	Offer positive reinforcement and explore ways of coping with obstacles Encourage self-rewards to positively reinforce change
Maintenance	Help patient maintain motivation Review identifying high-risk situations and strategies for preventing relapse	Discuss progress and signs of impending relapse
Relapse	Help patient view relapse as a learning experience Provide support appropriate to present level of readiness post-relapse	Offer a non-judgmental discussion about circumstances surrounding relapse and how to avoid relapse in the future Reassess patient's readiness to change

Adapted from Hunt P. Motivating Change. *Nursing Standard* 2001; 16(2):45-52, 54-55.

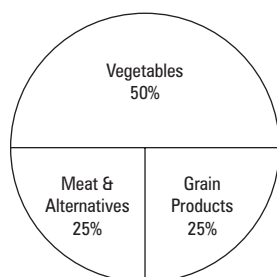


Figure 1. Plate Layout

**Handy Serving Size Comparisons**

- 3 oz meat, fish, poultry → palm of hand
- 1 cup dairy (milk/yogurt) → size of fist
- Bread/grains → one slice, palm of hand
- ½ cup rice/pasta → one hand cupped
- 1 cup of fruit/vegetables → two cupped hands
- 1 oz cheese → full length of thumb
- 1 tsp oil/butter → tip of thumb
- Nuts/chips/snacks → palm covered

**Energy Content of Food**

- Carbohydrates 4 kcal/g
- Protein 4 kcal/g
- Fat 9 kcal/g
- Ethanol 7 kcal/g

**Calculating Total Daily Energy Expenditure (TDEE)**

- Roughly 35 kcal/kg/day
- Varies by age, weight, sex, and activity level
- Average 2000-2100 kcal/d for women, 2700-2900 kcal/d for men

**Canadian Cancer Society (CCS) Recommendations for Vitamin D Use**

- Based on CCS research on Vitamin D and the prevention of colorectal, breast and prostate cancer.
- In consultation with their healthcare provider, the Society is recommending that:
 - Adults living in Canada should consider taking Vitamin D supplementation of 1,000 international units (IU) a day during the fall and winter.
 - Adults at higher risk of having lower Vitamin D levels should consider taking Vitamin D supplementation of 1,000 IU/day all year round. This includes people: who are older, with dark skin, who don't go outside often, and who wear clothing that covers most of their skin.

Nutrition

General Population

- Canada's Food Guide is appropriate for individuals >2 years old
- counsel on variety, portion size, and plate layout (see Figure 1)

Table 3. Canada's Food Guide 2007 Recommendations for Adults

Food Group	Servings/day	Choose More Often
Grain products	6-8	Whole grain and enriched grain products
Vegetables and fruit	7-10	Dark green vegetables, orange vegetables and fruit
Milk products	2-3 Children 2-8 years: 2 Youth 9-18 years: 3-4 Pregnant/breastfeeding: 3-4	Lower-fat dairy products
Meat and alternatives	2-3	Lean meat, poultry, fish, peas, beans, lentils

Cardiovascular Disease Prevention**Table 4. Dietary Guidelines for Reducing Risk of Cardiovascular Disease in General Population**

Food Item	Recommendations	Effects
Fat	Fat intake <30% of total energy Saturated fat <7% of energy Trans fat <1% of energy Cholesterol <300 mg/d	Lower LDL
Omega-3 fatty acid rich foods	≥2 servings/wk of fish (esp. oily fish like salmon)	Decreased: sudden death, death from CAD Lower TG
Salt	<6 g/d (100 mmol or 2.3 g/d of sodium)	Lower BP
Alcohol	≤2 drinks/d for men ≤1 drink/d for women	Excess alcohol increases risk of hypertriglyceridemia, HTN

References: Canada's Food Guide to Healthy Eating. Health Canada. Last updated 2007. <http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/>
 Lichtenstein AH, et al. (2006). Diet and lifestyle recommendations revision 2006: A scientific statement from the American Heart Association Nutrition Committee. Circulation, 114: 82-96.

Table 5. Introduction to Vitamins and Minerals

Vitamin/Mineral	Dietary Source	Signs of Deficiency	Signs of Toxicity
Folate (vit B₉)	Green leafy vegetables, organ meats, dried yeast, dried beans, legumes, citrus, fortified grains	Macrocytic anemia, diarrhea, glossitis, lethargy, stomatitis	None known from foods; seizures
Cyanocobalamin (vit B₁₂)	Meats, organ meats, beef, pork, milk, cheese, fish	Megaloblastic anemia, glossitis, leukopenia, weakness, peripheral neuropathy (esp. foot drop)	None known from foods
Ascorbic acid (vit C)	Citrus fruits, tomatoes, potatoes, red berries, peppers	Scurvy, keratosis of hair follicles, impaired wound healing, anemia, depression, lethargy, bleeding	Osmotic diarrhea, N/V, oxalate kidney stones, interference with anticoagulation therapy
Vitamin A	Fish liver oils, egg yolk, dairy products, green leafy or orange/yellow vegetables and fruit	Dermatitis, night blindness, keratomalacia, xerophthalmia	N/V, headache, dizziness, deep bone pain, peeling skin, gingivitis, alopecia, hepatotoxicity
Vitamin D	Fish, fish liver oils, fortified milk, egg yolk, sunlight	Osteomalacia, muscle weakness, bone pain, hypophosphatemia, hypocalcemia	Excess bone and soft tissue calcification, kidney stones, hypercalcemia, anorexia, renal failure
Vitamin E	Polyunsaturated vegetable oils, nuts, eggs, wheat germ, whole grains	Rare hemolysis, anemia, neuronal axonopathy, myopathy	Prolonged clotting time, impaired neutrophil function
Vitamin K	Green leafy vegetables, liver, vegetable oils, intestinal flora	Bleeding, purpura, bruising, prolonged clotting time	Jaundice
Calcium	Dairy products, dark, green and leafy vegetables, fortified soy, fortified orange juice	Tetany, arrhythmias, congestive heart failure, altered nerve conduction, osteomalacia	Metastatic calcification, weakness, renal failure, psychosis

Table 5. Introduction to Vitamins and Minerals (continued)

Vitamin/Mineral	Dietary Source	Signs of Deficiency	Signs of Toxicity
Magnesium	Soy, clams, wheat germ, almonds, dairy products, green leaves, nuts, cereal grains, seafood	Weakness, convulsions, neuromuscular irritability and dysfunction, failure to thrive	Hypotension, cardiac disturbances, respiratory failure
Potassium	Meat, milk, bananas, prunes, raisins, orange, grapefruit, potatoes, legumes	Polyuria, impaired muscle contraction, ECG changes (prolonged QT interval, prominent U-waves), peritoneal distention, dyspnea, paralysis, cardiac disturbances	Mental confusion, hypotension, weakness, ECG changes (flattened P-waves, peaked T-waves), paralysis, cardiac disturbances
Iron	Meat, fish, poultry, organ meats, eggs, prunes, peas, beans, lentils, soy, raisins, fortified grain products	Glossitis, fatigue, tachycardia, microcytic hypochromic anemia, koilonychia, enteropathy	Nutritional hemosiderosis, organ damage

Adapted from Mosby's Family Practice Sourcebook: *An Evidence-Based Approach to Care*, 4th edition, edited by Dr. Michael Evans (pp. 343-345). Copyright © 2006 Elsevier Canada, a division of Reed Elsevier Canada, Ltd. All rights reserved. Reprinted by permission of Elsevier Canada, 2009.

Table 6. Macronutrient Distribution Ranges

Age (years)	Macronutrient as % of Daily Calories		
	Protein	Fat	Carbohydrate
1 to 3	5 - 20	30 - 40	45 - 65
4 to 18	10 - 30	25 - 35	45 - 65
19 and older	10 - 35	20 - 35	45 - 65

Adapted from Dietary Reference Intakes Tables, Health Canada. http://www.hc-sc.gc.ca/fn-an/nutrition/reference/table/index_e.html

Obesity

- body mass index (BMI) = weight (kg)/height (m)² = weight (lbs)/height (inch)² x 703
- waist circumference (WC)
 - should be measured in all adults to assess obesity-related health risks
 - specific cutoff points exist for different ethnic backgrounds (as recommended by the 2006 Canadian Clinical Practice Guidelines on obesity)
 - measurement of waist-hip ratio has no advantage over waist circumference alone

Table 7. Classification of Weight by BMI, Waist Circumference, and Associated Disease Risks in Adults

	BMI (kg/m ²)	Obesity Class	Men ≤102 cm (40 in) Women ≤88 cm (35 in)	Men >102 cm (40 in) Women >88 cm (35 in)
Underweight	<18.5		—	—
Normal	18.5-24.9		—	—
Overweight	25.0-29.9		Increased	High
Obesity	30.0-34.9	I	High	Very High
	35.0-39.9	II	Very High	Very High
Extreme Obesity	40.0 +	III	Extremely High	Extremely High

From: Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risks, National Institute of Health, National Heart Lung and Blood Institute, Obesity Education Initiative, http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/bmi_dis.htm

Epidemiology

- 16% (4 million) of people ≥18 years old are obese, 32% (8 million) are overweight in Canada, according to StatsCan (2007)
- obesity rate in people of aboriginal origin is 1.6 times higher than the national average
- proportion of children aged 6-11 who are overweight has more than doubled in the last 25 years; percentage of overweight adolescents has tripled
- overweight and obesity rates in children are directly proportional to screen time (see *Exercise*, FM7)
- only 10-15% of population consume <30% fat daily
- obese persons generally consume more energy-dense food which tends to be highly processed, micronutrient poor, and high in fats, sugars, or starch



Burning Fat

3500 kcal of energy are produced for every pound of human fat burned during activity.



Losing Weight

- Aim for caloric intake 500-1000 kcal/d less than total daily energy expenditure (TDEE)
- Results in 1-2 lb (0.5-1 kg) weight loss per week
- Achieved by combination of increased activity and/or decreased caloric intake



Low BMI is Associated with:

- Osteoporosis
- Eating disorders
- Under-nutrition
- Pregnancy complications



Adverse Medical Consequences of Obesity

- Type 2 DM
- CAD
- Stroke
- HTN
- Gallbladder disease
- Non-alcoholic steatohepatitis
- Complications of pregnancy
- Dyslipidemia
- Osteoarthritis
- Sleep apnea
- Certain cancers
- CHF
- Low back pain
- Increased total mortality

"The Latest Evidence on Fad Diets..."
Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for Weight Loss and Heart Disease Risk Reduction
JAMA 2005; 293(1):43-53
Purpose: To assess the effectiveness and adherence rates of four popular diets for weight loss and reduction of cardiac risk factors.
Study Characteristics: Single center RCT at academic medical center in Boston, MA; 160 participants were randomized to either Atkins (carbohydrate restriction), Zone (macronutrient balanced and low glycemic load), Weight Watchers (low calorie/portion size), or Ornish (fat restriction) diet groups for a period of 18 months.
Participants: Adults aged 22 to 72 years with known HTN, dyslipidemia, or fasting hyperglycemia.
Results: Assuming that participants who discontinued the study remained at baseline, the mean weight loss at 1 year (and self selected dietary adherence rates per self report) were 2.1 kg for Atkins (53% of participants completed, $P=0.009$), 3.2 kg for the Zone (65% of participants completed, $P=0.002$), 3.0 kg for Weight Watchers (65% completed, $P<0.001$), 3.3 kg for Ornish (50% completed, $P=0.007$). Each diet significantly reduced the LDL/HDL ratio by ~10% ($P<0.05$), with no significant effects on blood pressure or glucose. Amount of weight loss was associated with adherence level ($r = 0.60$; $P<0.001$) but not with diet type ($r = 0.07$; $P = 0.40$). Weight loss for each diet was significantly associated with reduction in levels of total/HDL cholesterol ($r=0.36$), C-reactive protein ($r=0.37$), and insulin ($r=0.39$), with no significant difference between diets.
Conclusion: Each popular diet was associated with modest weight loss and reduction of several cardiac risk factors. Adherence level, and not diet type, was the most important predictor of weight loss and cardiac risk factor reduction.

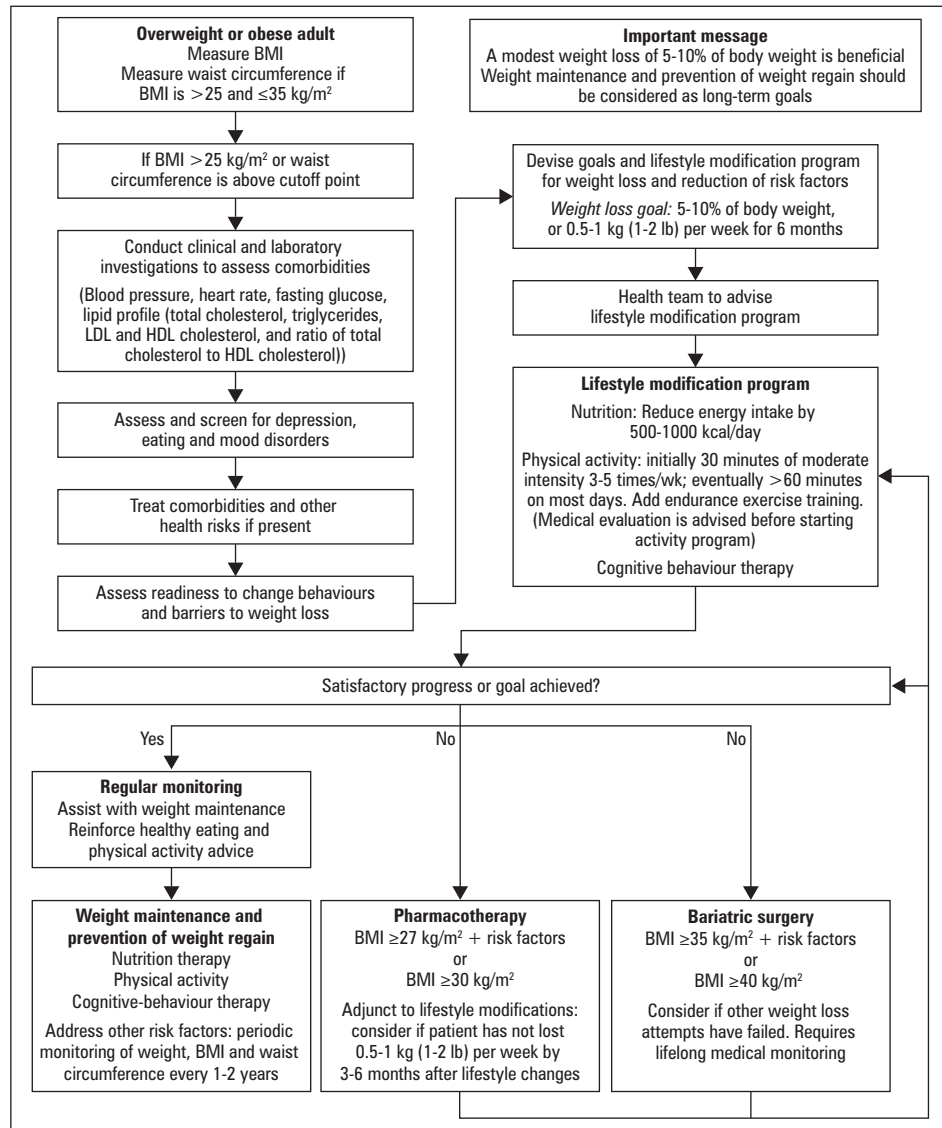


Figure 2. 2006 Canadian Clinical Practice Guidelines on the Management and Prevention of Obesity in Adults and Children (summary)
 Adapted from *CMAJ* 2007; 176:S1-S13.

Hyperlipidemia Signs

1. Atheromata – plaques in blood vessel walls
2. Xanthoma – plaques or nodules composed of lipid-laden histiocytes in the skin (esp. the eyelids)
3. Tendinous xanthoma – lipid deposit in tendon (esp. Achilles)
4. Corneal arcus (arcus senilis) – lipid deposit in cornea

LDL cannot be calculated when TG ≥4.5 mmol/L.

Clinical Definition of Metabolic Syndrome

- Central obesity
 - Men – waist circumference ≥94 cm
 - Women – waist circumference ≥80 cm
- plus any TWO of the following four factors:

Risk Factor	Defining Level
TG level	≥1.7 mmol/L (150 mg/dL)
HDL-C level:	
Men	<1.0 mmol/L (40 mg/dL)
Women	<1.3 mmol/L (50 mg/dL)
Blood pressure	≥130/85 mmHg
Fasting glucose level	≥5.6 mmol/L (100 mg/dL)

Dyslipidemia

- see [Endocrinology](#), E2
- defined as abnormal elevation of plasma cholesterol or triglyceride levels
- increased risk associated with obesity, DM, alcohol use

Assessment

- measure fasting serum TC, LDL-C, HDL-C, and TG
- screen with full fasting lipid profile in males over age 40, females over age 50 or who are menopausal, or any adults with additional CAD risk factors q1-3yrs
- assess for presence of other CAD risk factors
- screen for secondary causes: hypothyroidism, chronic kidney disease, DM, nephrotic syndrome, liver disease
- risk category
 - estimate using the model for 10-year CAD risk developed from the Framingham data
 - primary target of therapy is LDL-C levels; the alternate primary target is ApoB
 - optional secondary targets once LDL-C/apoB is at target include apoB:apoAI ratio, TC:HDL-C ratio, hs-CRP, non-HDL-C and serum TG levels
- emerging risk factors (from Framingham group)
 - lipoprotein a
 - metabolic syndrome
 - genetic risk
 - hormone replacement therapy
 - infectious agents

Table 8. Target Lipid Values for Primary Prevention of CAD in mmol/L (mg/dL)

Risk Category	Initiate Treatment if:	Primary Targets	
		LDL-C	Alternate
High (10-yr risk of CAD $\geq 20\%$, or history of DM or any atherosclerotic disease)	Consider treatment in all patients	$< 2 \text{ mmol/L}$ or $\geq 50\%$ decrease in LDL-C	$\text{apoB} < 0.80 \text{ g/L}$
Moderate (10-yr risk 11-19%)	LDL-C $> 3.5 \text{ mmol/L}$ TC/HDL-C > 5.0 Hs-CRP $> 2 \text{ mg/L}$ Men > 50 years Women > 60 years	$< 2 \text{ mmol/L}$ or $\geq 50\%$ decrease in LDL-C	$\text{apoB} < 0.80 \text{ g/L}$
Low (10-yr risk $\leq 10\%$)	LDL-C $\geq 5.0 \text{ mmol/L}$	$\geq 50\%$ decrease in LDL-C	

Reference: J Genest, R McPherson, J Frohlich, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations. *Can J Cardiol* 2009; 25(10):567-579.

Management

- intensity and type of treatment is guided by “risk category” assigned
- 1. health behaviours (can decrease LDL-C by up to 10%)
 - smoking cessation – probably the most important for preventing CAD
 - dietary modification – reduce saturated fats, refined sugars, alcohol; increase fruits, vegetables and fibres
 - physical activity – 30-60 min of moderate to vigorous activity on most days
 - employ consistent lifestyle modifications for at least 3 months before considering drug therapy; high risk patient should start treatment immediately with concurrent health behaviour interventions
- 2. pharmacologic therapy (can decrease LDL-C by up to 40%)
 - for a comparison of dyslipidemia medications, see Endocrinology, E5
 - statins (HMG-CoA reductase inhibitors)
 - currently recommended as 1st line monotherapy following unsuccessful lifestyle modifications
 - risks: myopathy and hepatotoxicity – must follow LFTs every 6 months
 - other agents: bile acid sequestrants, nicotinic acid, fibrates, psyllium, cholesterol absorption inhibitors (e.g. ezetimibe)
- after initiating drug therapy
 - fasting lipids should be measured after 6 weeks, and at 3 months
 - if adequate response is achieved, evaluate fasting lipids q4-6months
 - monitor ALT, AST, CK at baseline then 6 weeks later for signs of transaminitis or myositis; tolerate rise in CK within 10 times upper limit of normal, or creatinine of $\leq 25\%$; repeat ALT, AST and CK with lipid bloodwork
- isolated hypertriglyceridemia
 - normal HDL-C and TC, elevated TG
 - mild $\geq 2.2 \text{ mmol/L}$ ($\geq 200 \text{ mg/dL}$); marked $\geq 5.6 \text{ mmol/L}$ ($\geq 500 \text{ mg/dL}$)
 - principal therapy is lifestyle modifications
 - weight loss, exercise, avoidance of smoking and alcohol, effective blood glucose control in diabetics, increased omega-3 fatty acid intake
 - drug therapy
 - nicotinic acid
 - fibrates

Exercise

Epidemiology

- 25% of population exercises regularly, 50% occasionally, 25% sedentary
- screen time (time spent watching TV/movies, playing video games, or using the computer) has been increasing steadily in the last several years, while time spent being physically active has been decreasing
- excessive screen time can lead to obesity, encourage violent and antisocial behaviours, and foster attention deficit difficulties
- current recommendation from international pediatric societies is that children (> 2 years old) should limit their screen time to less than 2 hours/day

Model for Calculating the 10-year Risk of CAD in a Patient Without Diabetes Mellitus or Clinically Evident Cardiovascular Disease*, Using Framingham Data

STEP 1: DETERMINE RISK POINTS

Risk Factor	Risk Points		Risk Factor	Risk Points	
	Men	Women		Men	Women
Age, year					
30-34	-1	-9	55-59	4	7
35-39	0	-4	60-64	5	8
40-44	1	0	65-69	6	8
45-49	2	3	70-74	7	8
50-54	3	6			
Total cholesterol level, mmol/L					
< 4.14	-3	-2	6.22-7.24	2	2
4.15-5.17	0	0	≥ 7.25	3	3
5.18-6.21	1	1			
HDL-C level, mmol/L					
< 0.90	2	5	1.30-1.55	0	0
0.91-1.16	1	2	≥ 1.56	-2	-3
1.17-1.29	0	1			
Systolic blood pressure, mmHg					
< 120	0	-3	140-159	2	2
120-129	0	0	≥ 160	3	3
130-139	1	1			
Smoker					
No	0	0	Yes	2	2

STEP 2: CALCULATE RISK**

Total Risk Points	10-year Risk, %		Total Risk Points	10-year Risk, %	
	Men	Women		Men	Women
1	3	2	10	25	10
2	4	3	11	31	11
3	5	3	12	37	13
4	7	4	13	45	15
5	8	4	14	≥ 53	18
6	10	5	15		20
7	13	6	16		24
8	16	7	17		> 27
9	20	8			

*For example, a 55-year-old man who has a total cholesterol level of 5.43 mmol/L, an HDL-C level of 1.23 mmol/L, a systolic blood pressure of 148 mmHg and who smokes would have a total risk score of 9. His 10-year risk for CAD would be 20%, the risk for the average person of his age in the study population is 16%.

**Risk of CAD outcomes including angina pectoris, unstable angina, nonfatal myocardial infarction and coronary death over subsequent 10 years for a Framingham Study participant with that specific risk score.

Reference: Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: Summary of the 2003 update. *CMAJ* 2003; 169(1):921-924.

Comparative Tolerability of HMG-CoA Reductase Inhibitors

Drug Safety 2000; 23(3):197-213

Study: Review

Results: 1. There is no evidence to support that statin therapy leads to increased incidence of cataract formation. 2. Statin therapy does not lead to statistically significant disturbance in sleep or cognition compared to placebo. 3. The incidence of hepatotoxicity and elevated transaminases depends on statin dose. In general, all statins are similar in their rates of liver toxicity. 4. Statins metabolized solely by CYP3A4 (e.g. lovastatin, simvastatin, atorvastatin, cerivastatin) are more likely to result in hepatotoxicity or rhabdomyolysis if used in combination with a CYP3A4 inhibiting drug (e.g. ketoconazole, grapefruit juice, erythromycin).

Incidence of Hospitalized Rhabdomyolysis in Patients Treated with Lipid-Lowering Drugs

JAMA 2004; 292(21):2585-2590

Study: Retrospective cohort study.

Patients: 252460 patients treated with lipid-lowering agents.

Main outcome: Rhabdomyolysis requiring hospitalization.

Results: Of 252460 patients, 24 cases of rhabdomyolysis requiring hospitalization occurred. Incidence rates per 10000 person-years with 95% CI for each statin monotherapy are:

Atorvastatin 0.54 (0.22-1.12)

Cerivastatin 5.34 (1.46-13.68)

Pravastatin 0 (0-1.11)

Simvastatin 0.49 (0.06-1.76)

Fenofibrate 0 (0-14.58)

Gemfibrozil 3.70 (0.76-10.82)

Incidence of rhabdomyolysis increased to 5.98 (95% CI, 0.72-216.0) if atorvastatin, pravastatin or simvastatin was used with a fibrate, and up to 1035 (95% CI, 389-2117) if cerivastatin was combined with a fibrate.



Use with caution when prescribing combined statin and fibrate therapy as there has been recent concerns regarding the safety of certain combinations.

Management

- assess current level of fitness, motivation and access to exercise
- encourage warm up and cool down periods to allow transition between rest and activity and to avoid injuries
- exercise with caution for patients with CAD, diabetes (risk of hypoglycemia), exercise-induced asthma
- balanced exercise program incorporating all types of exercise
 1. aerobic (endurance) exercise for 15-60 min, 4-7 times/wk
 - ♦ improves cardiac function, lowers BP, increases HDL, increases insulin sensitivity
 - ♦ target HR: 60-80% of maximum HR
 - ♦ maximum HR=220-age
 2. weight-bearing (isometric) exercise 10-20 min, 2-4 times/wk
 - ♦ builds muscle strength, improves bone density, improves posture
 3. stretching routine 10-12 min, 4-7 times/wk
 - ♦ prevents cramps, stiffness, injuries, back problems
- other benefits of exercise
 - improves feeling of well-being, libido, quality of sleep, self-esteem
 - decreases depression and anxiety
 - weight control

Smoking Cessation

Physician Advice for Smoking Cessation

Cochrane Database of Systematic Reviews 2008; Issue 2

This systematic review of 17 trials compared brief advice by the physician versus no advice.

Reviewers' conclusions: Simple advice can increase cessation rates by 1 to 3%. More intensive advice and providing follow-up support may further increase the quit rates.



The 5 As for Patients Willing to Quit

Ask if patient smokes
Advise patient to quit
Assess willingness to quit
Assist in quit attempt
Arrange follow-up



Assist Patient in Developing Quit Plan

STAR
Set quit date
Tell family and friends (for support)
Anticipate challenges (e.g. withdrawal)
Remove tobacco products (e.g. ashtrays/lighters)

Epidemiology

- smoking is the single most preventable cause of premature illness and death
- 70% of smokers see a physician each year
- 2008 Canadian data from the Canadian Tobacco Use Monitoring Survey (CTUMS) on population age 15 or older
 - 18% are current smokers (lowest since 1965)
 - highest prevalence in age group 20-24 (28%)
 - 15% of youth aged 15-19 smoke (decreased from 25% in 2000): more males smoke than females (18% vs. 13%; 23% vs. 27% in 2000), cigarettes consumed per day also decreasing
 - in 2006, smoking rate decreased significantly among youth aged 15-19, from 18% down to 15%

Management

- **general approach**
 - identify tobacco users, elicit smoking habits, previous quit attempts and results
 - every smoker should be offered treatment
 - make patient aware of withdrawal symptoms
 - ♦ low mood, insomnia, irritability, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite
 - ≥4 counselling sessions >10 min each with 6-12 month follow-up yield better results
 - 14% abstinent with counselling vs. 10% without counselling (OR 1.55)
 - approach depends on patient's stage of change (see *Motivational Strategies for Behavioural Change*, FM3)
- **willing to quit**
 - follow the 5 As (see sidebar)
 - provision of social support, community resources
 - pregnant patients: advise to quit first without pharmacotherapy; use pharmacotherapy only if benefits > risks; consult Motherisk
 - Nicotine Replacement Therapy (NRT)
 - ♦ 19.7% abstinent at 12 months with NRT vs. 11.5% for placebo (OR 1.66)
 - ♦ no difference in achieving abstinence for different forms of NRT
 - ♦ reduces cravings and withdrawal symptoms without other harmful substances that are contained in cigarettes
 - ♦ use with caution: immediate post-MI, serious/worsening angina, serious arrhythmia
 - Bupropion SR (Zyban®)
 - ♦ 21% abstinent at 12 months vs. 8% for placebo (OR 2.73)
 - Varenicline (Champix®)
 - ♦ partial nicotinic receptor agonist (to reduce cravings) and partial competitive nicotinic receptor antagonist (to reduce the response to smoked nicotine)
 - ♦ more effective than bupropion

Table 9. Types of Nicotine Replacement Therapy

Type	Dosage	Comment	Side Effects
Nicotine Gum (OTC)	2 mg if <25 cig/d 4 mg if >25 cig/d 1 piece q1-2h for 1-3 mos (max. 24 pieces/d)	Chew until "peppery" taste then "park" between gum and cheek to facilitate absorption Continue to chew-park intermittently for 30 min	Mouth soreness Hiccups Dyspepsia Jaw ache Most SE's are transient
Nicotine Patch (OTC)	Use for 8 weeks 21 mg/d x 4 weeks 14 mg/d x 2 weeks 7 mg/d x 2 weeks	Start with lower dose if <10 cig/d Change patch q24h and alternate sides	Skin irritation Insomnia Palpitations Anxiety
Nicotine Inhaler (OTC)	6-16 cartridges/day for up to 12 weeks	Nicotine inhaled through mouth, absorbed in mouth and throat but not in lungs	Local irritation Coughing
Nicotine Nasal Spray (Rx)		Not available in Canada	

Nicotine Replacement Therapy for Smoking Cessation

Cochrane Database of Systematic Reviews 2008; Issue 1

This systematic review of 132 randomized trials compared NRT to placebo or no treatment or compared different NRT doses.

Reviewers' conclusions: All commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) are effective as part of a strategy to promote smoking cessation. They increase the rate of quitting by 50 to 70% regardless of setting and independent on the level of additional support provided to the smoker. Compared to a single form of NRT, combining a nicotine patch with a rapid delivery form of NRT may be more effective.

Table 10. Bupropion as Treatment for Smoking Cessation

Mechanism	Dosage	Prescribing*	Contraindications
Inhibits re-uptake of dopamine and/or norepinephrine	1. 150 mg qAM x 3 days 2. Then 150 mg bid x 7-12 wks 3. For maintenance consider 150 mg bid for up to 6 months	1. Decide on a quit date 2. Continue to smoke for first 1-2 wks of treatment and then completely stop (therapeutic levels reached in 1 wk)	Seizure disorder Eating disorder MAOI use in past 14 days Simultaneous use of bupropion (Wellbutrin®) for depression

*May be used in combination with nicotine replacement therapy

Antidepressants for Smoking Cessation

Cochrane Database of Systematic Reviews 2007; Issue 1

This systematic review of 66 randomized trials compared antidepressant medication to placebo or alternative pharmacotherapy for smoking cessation and where follow-up was longer than 6 months.

Reviewers' conclusions: The antidepressants bupropion and nortriptyline can aid smoking cessation and have a similar efficacy to NRT. Compared to bupropion, varenicline showed higher quit rates. Selective serotonin reuptake inhibitors (e.g. fluoxetine) or venlafaxine did not have a significant effect.

Table 11. Varenicline as Treatment for Smoking Cessation

Mechanism	Dosage	Prescribing*	Contraindications
Partial nicotinic receptor agonist, and partial competitive antagonist nicotinic receptor	1. 0.5 mg qAM x 3 days 2. Then 0.5 mg bid x 4 days 3. Continue 1 mg BID x 12 weeks plus ± additional 12 weeks as maintenance	Begin treatment 1 week before quit date, then stop smoking as planned	Caution with pre-existing psychiatric condition

*May be used in combination with nicotine replacement therapy

• unwilling to quit

- motivational intervention (5 Rs) (see sidebar):

1. Risks of smoking

- ♦ short-term: SOB, asthma exacerbation, impotence, infertility, pregnancy complications, heartburn, URTI
- ♦ long-term: MI, stroke, COPD, lung CA, other cancers
- ♦ environmental: higher risk in spouse/children for lung CA, SIDS, asthma, respiratory infections

2. Rewards: benefits

- ♦ improved health, save money, food tastes better, good example to children

3. Road blocks: obstacles

- ♦ fear of withdrawal, weight gain, failure, lack of support

4. Repetition

- ♦ reassure unsuccessful patients that most people try many times before successfully quitting (average number of attempts before success is 7)

• recent quitter

- highest relapse rate within 3 months of quitting

- ♦ minimal practice: congratulate on success, encourage ongoing abstinence, review benefits, problems
- ♦ prescriptive interventions: address problems of weight gain, negative mood, withdrawal, lack of support

**The 2-3 Pattern of Smoking Cessation**

- Onset of withdrawal is 2-3 hours after last cigarette
- Peak withdrawal is at 2-3 days
- Expect improvement of withdrawal symptoms at 2-3 weeks
- Resolution of withdrawal at 2-3 months
- Highest relapse rate within 2-3 months

**The 5 Rs for Patients Unwilling to Quit**

Relevance to patient (health concerns, family/social situations)

Risks of smoking

Rewards of quitting

Roadblocks to quitting

Repetition of motivational intervention at each visit

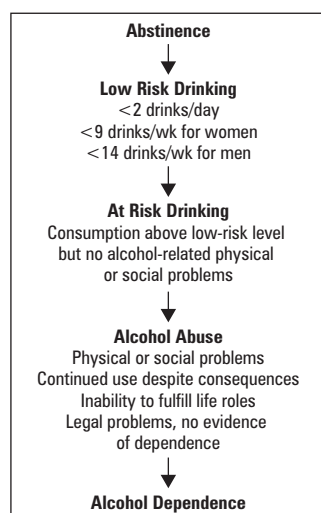


Figure 3. Continuum of Alcohol Use

**Standard Drink Equivalents**

One standard drink = 14 g of pure alcohol

- Beer (5% alcohol) = 12 oz
- Wine (12-17% alcohol) = 5 oz
- Fortified wine = 3 oz
- Hard liquor (80 proof) = 1.5 oz

**CAGE Questionnaire**

- C** Have you ever felt the need to **CUT** down on your drinking?
A Have you ever felt **ANNOYED** at criticism of your drinking?
G Have you ever felt **GUILTY** about your drinking?
E Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?
(EYE OPENER)

≥2 for men or ≥1 for women suggests possibility of problem drinking (sensitivity 85%, specificity 89%)

**Alcohol Metabolized per Hour**

- Alcohol metabolism is constant (zero-order kinetics) regardless of blood alcohol level (BAL)
- Average metabolism ranges between 13-25 mg/dL blood/hour or 100-200 mg/kg/hour
- Equivalent to metabolizing 0.5-1 standard drink per hour or BAL decrease of 0.01% per hour
- Metabolism more rapid in chronic alcoholics

**Some Adverse Medical Consequences of Problem Drinking**

- GI: gastritis, dyspepsia, pancreatitis, liver disease, bleeds, diarrhea, oral/esophageal cancer
- Cardiac: hypertension, alcoholic cardiomyopathy
- Neurologic: Wernicke-Korsakoff syndrome, peripheral neuropathy
- Hematologic: anemia, coagulopathies
- Other: trauma, insomnia, family violence, anxiety/depression, social/family dysfunction, sexual dysfunction, fetal damage

Alcohol

- see Psychiatry, PS20

Definition

- diagnostic categories occur along a continuum (see Figure 3)

Epidemiology

- 10-15% of patients in family practice are problem drinkers
- 20-50% of hospital admissions, 10% of premature deaths, 30% of suicides, and 50% of fatal traffic accidents in Canada are alcohol-related
- more likely to miss diagnosis in women, elderly, patients with high socioeconomic status

Assessment

- screen for alcohol dependence with CAGE questionnaire (see sidebar)
 - if CAGE positive, explore with further questions for alcohol abuse
- assess drinking profile
 - setting, time, place, occasion, with whom
 - impact on: family, work, social
 - quantity-frequency history
 - ♦ how many drinks per day?
 - ♦ how many days per week?
 - ♦ maximum number of drinks on any one day in the past month?
- if identified positive for alcohol problem
 - screen for other drug use
 - identify medical/psychiatric complications
 - ask about drinking and driving
 - ask about past recovery attempts and current readiness for change

Investigations

- GGT and MCV for baseline and follow-up monitoring
- AST, ALT (usually AST:ALT approaches 2:1 in an alcoholic)
- CBC (anemia, thrombocytopenia), INR (decreased clotting factors production by liver)

Management

- intervention should be consistent with patient's motivation for change
- regular follow-up is crucial
- 10% of patients in alcohol withdrawal will have seizures or delirium tremens
- Alcoholics Anonymous/12-step program
 - outpatient/day programs for those with chronic, resistant problems
 - family treatment (Al-Anon, Alateen, screen for spouse/child abuse)
- in-patient program if
 - dangerous or highly unstable home environment
 - severe medical/psychiatric problem
 - addiction to drug that may require in-patient detoxification
 - refractory to other treatment programs
- pharmacologic
 - diazepam for withdrawal
 - disulfiram (Antabuse®): impairs metabolism of alcohol by blocking conversion of acetaldehyde to acetic acid, leading to flushing, headache, nausea/vomiting, hypotension if alcohol is ingested
 - naltrexone: competitive opioid antagonist that reduces cravings and pleasurable effects of drinking
 - ♦ may trigger withdrawal in opioid-dependent patients

Prognosis

- relapse is common and should not be viewed as failure
- monitor regularly for signs of relapse
- 25-30% of abusers exhibit spontaneous improvement over 1 year
- 60-70% of individuals with jobs and families have an improved quality of life 1 year post-treatment

Common Presenting Problems

Abdominal Pain

- see Gastroenterology, G2 and General Surgery, GS4

Epidemiology

- 20% of individuals have experienced abdominal pain within the last 6-12 months
- 90% resolve in 2-3 weeks
- only 10% are referred to specialists, <10% admitted to hospital

Etiology

- most common diagnosis is “nonspecific abdominal pain,” which has no identifiable cause and is usually self-limited
- GI disorders (e.g. PUD, pancreatitis, IBD, appendicitis, gastroenteritis, IBS, diverticular disease, biliary tract disease)
- urinary tract disorders (e.g. UTI, renal calculi)
- gynecological disorders (e.g. PID, ectopic pregnancy, endometriosis)
- cardiovascular disorders (e.g. CAD, AAA, ischemic bowel)
- other: toxic ingestion, foreign body, psychogenic

Pathophysiology

- type of pain
 - somatic pain – sharp, localized pain
 - visceral pain – dull, generalized pain
- location of pain
 - epigastric (foregut) – distal esophagus, stomach, proximal duodenum, biliary tree, pancreas, liver
 - periumbilical (midgut) – distal duodenum to proximal 2/3 of transverse colon
 - hypogastric (hindgut) – distal 1/3 of transverse colon to rectosigmoid region

Investigations

- guided by findings on history and physical
- possible bloodwork: CBC, electrolytes, BUN, Cr, amylase, lipase, AST, ALT, ALP, bilirubin, glucose, INR/PTT, tox screen, beta-hCG
- imaging
 - abdominal x-ray (gas pattern, free air)
 - ultrasound (gallbladder disease, gynecological problems)
 - CT scan (AAA, appendicitis)
- other tests
 - urinalysis
 - endoscopy (for peptic ulcers, gastritis, tumours, etc.)
 - *H. pylori* testing (urea breath test, serology)



In patient >50 years old, keep a high index of suspicion for AAA – its presentation may mimic renal colic or diverticulitis.



If pain precedes nausea/vomiting, cause of abdominal pain is more likely to be surgical.

Allergic Rhinitis

- see Otolaryngology, OT23

Definition

- inflammation of the nasal mucosa that is triggered by an allergic reaction
- classification:
 - seasonal
 - ♦ symptoms during a specific time of the year
 - ♦ common allergens: trees, grass and weed pollens, airborne moulds
 - perennial
 - ♦ symptoms throughout the year with variation in severity
 - ♦ common allergens: dust mites, animal dander, moulds

Etiology

- increased IgE levels to certain allergens → excessive degranulation of mast cells → release of inflammatory mediators (e.g. histamine) and cytokines → local inflammatory reaction

**Differential Diagnosis**

- Acute viral infection
- Vasomotor rhinitis
- Deviated septum
- Nasal polyps
- Acute/chronic sinusitis
- Drug-induced rhinitis
- Pregnancy



Rhinitis medicamentosa – Rebound nasal congestion. Occurs with prolonged use (>5-7 days) of vasoconstrictive medications. Patient may become dependent, requiring more frequent dosing to achieve the same decongestant effect.

Epidemiology

- affects approximately 40% of children and 20-30% of adults
- prevalence has increased in developed countries, particularly in the past two decades
- associated with asthma, sinusitis, and otitis media

Assessment

- identify allergens
- take an environmental/occupational history
- ask about related conditions (e.g. atopic dermatitis, asthma, sinusitis, and family history)

Management

- conservative
 - minimize exposure to allergens
 - ♦ most important aspect of management, often sufficient (may take months)
 - maintain hygiene, saline nasal rinses
- pharmacologic agents
 - oral antihistamines – first line therapy for mild symptoms
 - ♦ e.g. cetirizine (Reactine®), fexofenadine (Allegra®), loratadine (Claritin®)
 - intranasal corticosteroids for moderate/severe or persistent symptoms (>1 month of consistent use to see results)
 - intranasal decongestants (use must be limited to <5 days to avoid rhinitis medicamentosa)
- allergy skin testing
 - for patients with chronic rhinitis
 - symptoms not controlled by allergen avoidance, pharmacological therapy
 - may identify allergens to include in immunotherapy treatment
- immunotherapy (allergy shots)
 - reserved for severe cases unresponsive to pharmacologic agents
 - consists of periodic (usually weekly) subcutaneous injections of custom prepared solutions of one or more antigens to which the patient is allergic

Amenorrhea

- see Gynecology, G12

Definition and Etiology

- classified as primary or secondary
 - primary
 - ♦ absence of menstruation by age 14 in women without secondary sexual characteristics, or absence of menstruation by age 16 in women with secondary sexual characteristics
 - ♦ causes: Turner's syndrome, constitutional delay of growth and puberty, Kallmann syndrome, androgen insensitivity syndrome, Mullerian agenesis, imperforate hymen, transverse vaginal septum, also include differential of secondary amenorrhea
 - secondary
 - ♦ absence of menstruation for 3 months in women with previously normal menstruation, or absence of menstruation for 9 months in women with previous oligomenorrhea
 - ♦ causes: pregnancy, hypothyroidism, hyperprolactinemia, medications, premature ovarian failure, anorexia or bulimia nervosa, CNS tumour, chronic illness, PCOS

Assessment

- history
 - menarche and menstrual history, sexual activity, exercise, weight loss, current or previous chronic illness, prescription/illicit drug use, previous CNS chemo or radiation, previous pelvic radiation, psychosocial stressors
 - family history of genetic defects, infertility, menarche and menstrual history, pubertal history
- physical
 - growth chart, BMI, Tanner staging, dysmorphic features (e.g. webbed neck, short stature), signs of Cushing's disease, thyroid exam, hirsutism or acne, pubic hair pattern, imperforate hymen, absent uterus

Investigations

- based on clinical picture
- consider beta-hCG, prolactin, TSH, progesterone challenge test, FSH and LH levels, head MRI, karyotype

Anxiety

- see Psychiatry, PS12

Epidemiology

- 25-30% of patients in primary care settings have psychiatric disorders
- many are undiagnosed or untreated; hence the need for good screening
- high rate of coexistence of anxiety disorders and depression

Screening

- screening questions
 - Do you tend to be an anxious or nervous person?
 - Have you felt unusually worried about things recently?
 - Has this worrying affected your life? How?
- if positive response, follow up with symptom-specific questions (see Figure 4)

Assessment

- associated symptoms
- risk factors
 - family history of anxiety or depression, past history of anxiety, stressful life event, social isolation, gender (women), co-morbid psychiatric diagnosis
- assess substance abuse, co-morbid depression, suicidal ideations/self-harm
- to differentiate anxiety disorders, consider symptoms and their duration (see Figure 4)



Differential Diagnosis (see Figure 4)

- Panic disorder
- GAD
- PTSD
- OCD
- Social phobia
- Specific phobia
- Separation anxiety (children)
- Other: GMC, mood disorder, psychotic disorder



Rule Out

- Cardiac (post MI, arrhythmias)
- Endocrine (hyperthyroidism, diabetes, pheochromocytoma)
- Respiratory (asthma, COPD)
- Somatoform disorders
- Psychotic disorders
- Mood disorders (depression, bipolar)
- Personality disorder (OCPD)
- Drugs (amphetamines, thyroid preparations, caffeine, OTC for colds/decongestants, alcohol/benzodiazepine withdrawal)

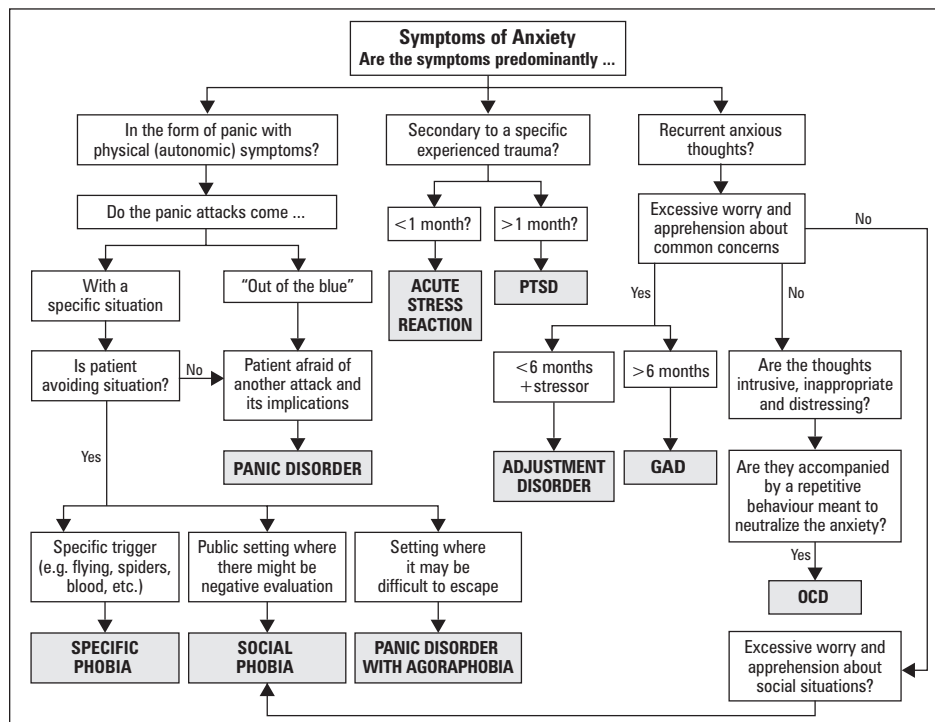


Figure 4. Differentiating Anxiety Disorders

Adapted from: Anxiety Review Panel. Evans M, Bradwejn J, Dunn L (Eds) (2000). *Guidelines for the Treatment of Anxiety Disorders in Primary Care*. Toronto: Queen's Printer of Ontario, pp. 41.

Management

- patient education: emphasize prevalence, good recovery rate of anxiety conditions
- lifestyle advice: decrease caffeine and alcohol intake, exercise, relaxation techniques
- self-help materials, community resources (e.g. support groups)
- cognitive behavioural therapy: cognitive interventions, exposure therapy, etc.
- pharmacotherapy
 - for GAD
 - ♦ 1st line – escitalopram, paroxetine, sertraline, venlafaxine XR
 - antidepressants better for depression and ruminative worry than benzodiazepines
 - ♦ 2nd line – benzodiazepines, bupropion XL, buspirone, imipramine, pregabalin
 - ♦ 3rd line – mirtazapine, citalopram, trazodone, hydroxyzine, adjunctive olanzapine, risperidone
 - 3rd line therapy may be used as an adjunct or used for those patients who fail 1st and 2nd line therapy alone or combined

- ♦ benzodiazepines can be used at any time for severe agitation/anxiety
 - due to side effects, dependence and withdrawal issues, benzodiazepines are best used on a short-term basis (i.e. 1-2 months)
- ♦ beta-blockers are not recommended
- ♦ therapy should continue for at least 1 year after relief of symptoms
- for pharmacotherapy specific to other types of anxiety, see [Psychiatry](#), PS13



Commonly feared situations include: public speaking, eating, drinking, writing in front of others, using public restrooms, speaking on the telephone and social gatherings.

SOCIAL PHOBIA

- a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others

Epidemiology

- lifetime prevalence rate of up to 16%; F:M = 1.5:1
- often begins in early childhood and adolescence
- can lead to significant psychiatric comorbidity including depression, other anxiety disorders, alcohol and substance abuse and eating disorders

History

- fear of being humiliated or embarrassed in one or more social or performance situations
- fear is recognized as excessive or unreasonable
- avoidance, anticipation and distress of the social situation interferes significantly with social and occupational functioning
- can often present with somatic complaints of insomnia, fatigue, palpitations, chest pain, shortness of breath, dizziness, trembling hands, sweating, blushing and GI complaints

Physical

- symptoms of hyperhidrosis, tremor, blushing, stuttering, hypertension and tachycardia
- thorough mental status examination

Management

- cognitive behavioural therapy
- exposure therapy, cognitive restructuring and social skills training to decrease anxiety and weaken the tendency to avoid social situations
 - exposure therapy is the most well established therapeutic technique
- pharmacotherapy
 - effective treatments include SSRIs, MAOIs and anxiolytics; no TCAs
 - SSRIs are preferred because of effectiveness and lack of significant side effects
 - beta-blocker or benzodiazepine in acute social situations

Asthma/COPD

- see [Respirology](#), R7

Definition

- asthma
 - chronic but reversible airway inflammation characterized by periodic attacks of wheezing, shortness of breath, chest tightness, and coughing
 - airways hyper-responsive to triggers/antigens leading to acute obstructive symptoms by bronchoconstriction, mucous plugs and increased inflammation
 - cannot be diagnosed at first presentation
 - pulmonary function tests can be done from age 6
 - peak flow meters are useful in the office for monitoring
 - called Reactive Airway Disease until recurrent presentations
- chronic obstructive pulmonary disease (COPD)
 - a group of chronic, progressive, expiratory lung diseases characterized by limited airflow with variable degrees of air sac enlargement and lung tissue destruction
 - emphysema and chronic bronchitis are the most common forms of COPD



Differential Diagnosis of Asthma

- Chronic obstructive pulmonary disease
- Cystic fibrosis
- Vocal cord dysfunction
- Congestive heart failure
- Mechanical obstruction of airways (e.g. tumours)

Table 12. Differentiating COPD from Asthma

	COPD	Asthma
Age of Onset	Usually in 6th decade	Any age (but 50% of cases diagnosed in children < 10 yo)
Role of Smoking	Directly related	Known trigger
Reversibility of Airflow Obstruction	Airflow obstruction is chronic and persistent	Airflow obstruction is episodic and usually reversible with therapy
Evolution	Slow, cumulative disabling pattern	Episodic, less than 50% will outgrow
History of Allergy	Infrequent	Over 50% patients
Precipitators	Environmental irritants (air pollution), cigarette smoking, antiprotease deficiency, viral infection, occupational exposure (firefighters, dusty jobs)	Environmental irritants (dust, pollen), furry animals, cold air, exercise, URTIs, cigarette smoke, use of beta-blockers/ASA
Symptoms/Signs	Chronic cough, sputum and/or dyspnea	Wheeze (hallmark symptom), dyspnea, chest tightness, cough which is worse in cold, at night, and in early AM prolonged expiration
Diffusion Capacity	Decreased (more so in pure emphysema)	Normal (for pure asthma)
Hypoxemia	Chronic in advanced stages	Not usually present Episodic with severe attacks
Spirometry	May have improvement with bronchodilators but not universally seen	Marked improvement with bronchodilators or steroids
Chest X-ray	Often normal Increased bronchial markings (chronic bronchitis) and chronic hyperinflation (emphysema) often co-exist	Often normal or episodic hyperinflation Hyperinflation during asthma attack
Management	First line: ipratropium bromide (Atrovent®) Others: salbutamol (Ventolin®), tiotropium bromide (Spiriva®), fluticasone (Flovent®), oral prednisone, oxygen, salmeterol (Serevent®) at bedtime Get flu shot and Pneumovax®	Combination of rescue medications (SABAs) taken on prn basis and maintenance medications (see sidebar) taken on a regular basis to achieve control of asthma symptoms Maintenance medications: Step 1: Low-dose ICS Step 2: Medium/high-dose ICS or low-dose ICS plus either LABA, LT modifier, or long-acting theophylline Step 3: Medium/high-dose ICS plus either LABA, LT modifier, or long-acting theophylline Step 4: As above plus immunotherapy ± oral glucocorticosteroids + flu shot and Pneumovax®

SABA = short-acting beta-agonist LABA = long-acting beta-agonist ICS = inhaled glucocorticosteroids LT modifier = leukotriene modifier



When prescribing Ventolin®, watch out for signs of hypokalemia: lethargy, irritability, paresthesias, myalgias, weakness, palpitations, nausea, vomiting, polyuria.



Signs of Poorly Controlled Asthma

- Beta-2 agonist use > 4x/wk
- Asthma-related absence from work/school
- Exercise induced asthma
- Night-time symptoms > 1x/wk



What Colour is Your Inhaler?

Name	Body/Cap Colour
Beta-2-agonists	
Ventolin®	light blue/navy
Serevent®	teal/light teal
Bricanyl®	blue/white
ICS	
Flovent®	orange/peach
Pulmicort®	white/brown
Combined	
Advair®	purple discus
Symbicort®	red/white
Other	
Atrovent®	clear/green
Combivent®	clear/orange
Spiriva®	white/turquoise

Benign Prostatic Hyperplasia (BPH)

- see Urology, U7

Definition

- hyperplasia of the stroma and epithelium in the periurethral transition zone

History and Physical

- include current/past health, surgeries, trauma, current and OTC meds (see Table 13)
- physical exam must include DRE for size, symmetry, nodularity, and texture of prostate (prostate is symmetrically enlarged, smooth and rubbery in BPH)

Investigations

- urinalysis for microscopic hematuria (common sign)
- serum PSA: protein produced by prostatic tissue
 - increased PSA in a younger man is more often due to cancer than other causes
 - an abnormality on DRE or PSA should trigger further assessment
 - discuss test with men at increased risk of prostate cancer (FHx, African ancestry) or who are concerned about development of prostate cancer
 - considered normal when <4.0 ng/mL; but must take into account patient's age and rate of PSA increase (PSA velocity)
 - if between 4-10 ng/mL: consider measuring free/total PSA
 - if >10 ng/mL, can diagnose prostate pathology
 - PSA testing is inappropriate in men with a life expectancy less than 10 years
 - PSA should not be measured in patients with an acute UTI



Differential Diagnosis

- Prostate cancer
- Urethral obstruction
- Bladder neck obstruction
- Neurogenic bladder
- Cystitis
- Prostatitis

- other
 - Cr, BUN
 - post-void residual volume by ultrasound
 - uroflow
 - patient voiding diary, International Prostate Symptom Score
- tests NOT recommended as part of routine initial evaluation include:
 - cystourethroscopy
 - cytology
 - prostate ultrasound or biopsy
 - IVP

Table 13. Symptoms of BPH

Obstructive Symptoms	Irritative Symptoms	Late Complications
Hesitancy (difficulty starting urine flow)	Urgency	Hydronephrosis
Diminution in size and force of urinary stream	Frequency	Loss of renal concentrating ability
Stream interruption (double voiding)	Nocturia	Systemic acidosis
Urinary retention (bladder does not feel completely empty)	Urge incontinence	Renal failure
Post-void dribbling	Dysuria	
Overflow incontinence		

Management

- referral to urologist if moderate to severe symptoms
- conservative: for patients with mild symptoms or moderate/severe symptoms considered by the patient to be non-bothersome
 - fluid restriction (avoid alcohol and caffeine)
 - avoidance/monitoring of certain medications (e.g. antihistamines, diuretics, antidepressants, decongestants)
 - pelvic floor exercises
 - bladder retraining – organized voiding
- pharmacological: for moderate/severe symptoms
 - alpha receptor antagonists [e.g. terazosin (Hytrin®), doxazosin (Cardura®), tamsulosin (Flomax®), alfuzosin (Xatral®)]
 - ♦ relaxation of smooth muscle around the prostate and bladder neck
 - 5-alpha reductase inhibitor [e.g. finasteride (Proscar®)]
 - ♦ only for patients with demonstrated prostatic enlargement due to BPH
 - ♦ inhibits enzyme responsible for conversion of testosterone into DHT thus reducing growth of prostate
 - phytotherapy (e.g. saw palmetto berry extract, *Pygeum africanum*)
 - ♦ more studies required before being recommended as standard therapy
 - ♦ considered safe
- surgical:
 - TURP: transurethral resection of the prostate
 - ♦ absolute indications: failed medical therapy, intractable urinary retention, benign prostatic obstruction leading to renal insufficiency
 - ♦ complications include: impotence, incontinence, ejaculatory difficulties (retrograde ejaculation), decreased libido
 - TUIP: transurethral incision of the prostate – for prostates <30 g
 - other invasive procedures: TUVAP (transurethral electrovaporization of prostate), laser prostatectomy, open prostatectomy
 - minimally invasive surgical therapies (MIS):
 - ♦ TUMT: transurethral microwave therapy
 - ♦ TUNA: transurethral needle ablation
 - ♦ stents: for severe urinary obstruction in non-surgical candidate

**Differential Diagnosis**

- URTI
- Asthma
- Acute exacerbation of chronic bronchitis
- Sinusitis
- Pneumonia
- Bronchiolitis
- Pertussis
- Environmental/occupational exposures
- Post-nasal drip
- Others: reflux esophagitis, CHF, bronchogenic CA, aspiration syndromes, CF, foreign body

Bronchitis (Acute)**Definition**

- acute infection of the tracheobronchial tree causing inflammation leading to bronchial edema and mucus formation

Epidemiology

- 5th most common diagnosis in family medicine, most common is URTI

Etiology

- 80% viral: rhinovirus, coronavirus, adenovirus, influenza, parainfluenza, RSV
- 20% bacterial: *M. pneumoniae*, *C. pneumoniae*, *S. pneumoniae*

Investigations

- acute bronchitis is typically a clinical diagnosis
- sputum culture/Gram stain is not very informative
- CXR if suspect pneumonia (cough >3 weeks, abnormal vital signs, localized chest findings) or CHF
- pulmonary function tests with methacholine challenge if suspect asthma

Management

- primary prevention: frequent hand washing, smoking cessation, avoid irritant exposure
- symptomatic relief: rest, fluids (3-4 L/day when febrile), humidity, analgesics and antitussives as required
- bronchodilators may offer improvement of symptoms (e.g. albuterol)
- current literature does not support routine antibiotic treatment for the management of acute bronchitis because it is most likely to be caused by a viral infection
 - antibiotics may be useful if elderly, comorbidities, pneumonia is suspected, or if the patient is toxic (refer to *Antimicrobial Quick Reference*, FM50)
 - antibiotics in children show no benefit



How to Tell if Viral or Bacterial?

Bacterial infections tend to give a higher fever, excessive amounts of purulent sputum production, and may be associated with concomitant COPD.

Note: purulent sputum is not necessarily bacterial.

Chest Pain

- see *Cardiology and Cardiovascular Surgery*, C4 and *Emergency Medicine*, ER22

Differential Diagnosis

Table 14. Differential Diagnosis of Chest Pain

Cardiac	Pulmonary	GI	MSK/Neuro	Psychologic
Angina*	Pneumonia	GERD	Costochondritis	Anxiety
MI*	Pneumothorax*	PUD	Intercostal strain	Panic
Pericarditis*	PE*	Perforated viscus*	Arthritis	Depression
Myocarditis	Pulmonary HTN	Esophageal spasm	Rib fractures	
Aortic dissection*	Lung CA	Cholecystitis	Herpes zoster	
Endocarditis		Hepatitis		

*Emergent



Risk Factors for Coronary Artery Disease

Major

1. Smoking
2. Diabetes
3. Hypertension
4. Hyperlipidemia
5. Family history

Minor

1. Obesity
2. Sedentary lifestyle
3. Age

Investigations

- ECG, CXR, and others if indicated (cardiac enzymes, D-dimers, LFTs, etc.)
- refer to Emergency Department if suspect serious etiology (e.g. aortic dissection, MI)

Management of Common Causes of Chest Pain

- angina/ischemic heart disease
 - acute: nitroglycerin (NTG) (wait 5 minutes between sprays and if no effect after 3 sprays, send to ER)
 - ♦ if inferior MI, NTG will cause patient to become hypotensive
 - long term: see Figure 5
- myocardial infarction (MI)
 - chew ASA STAT, to ER for "MONA" (Morphine, Oxygen, NTG, ASA)
 - ± reperfusion therapy with tPA or streptokinase if within 6 hours (Note: can only use SK once in lifetime)
 - start beta-blocker (e.g. metoprolol starting dose 12.5 mg PO OD, increase gradually to 50 mg PO bid)
- endocarditis: IV penicillin G 20 million units OD or IV ampicillin 12 g OD
- GERD: antacids, H₂ blockers, PPIs
- costochondritis: NSAIDs



High-Risk Symptoms and Signs of Chest Pain include:

- Severe pain
- Pain for >20 min
- New onset pain at rest
- Severe SOB
- Loss of consciousness
- Hypotension
- Tachycardia
- Bradycardia
- Cyanosis



MI in Elderly Women

Elderly women can often present with dizziness, lightheadedness or weakness, in the absence of chest pain.

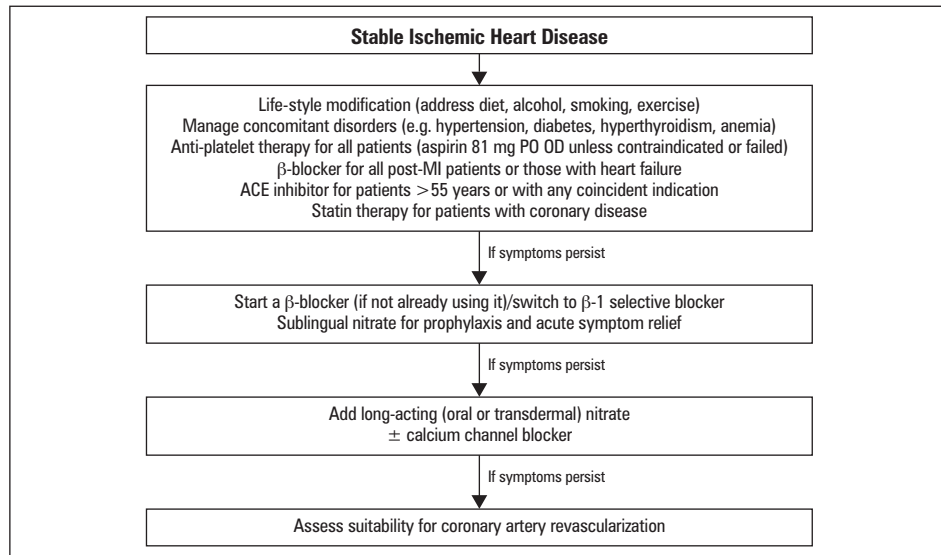


Figure 5. Treatment Algorithm for Stable Ischemic Heart Disease

References: Ontario Drug Therapy Guidelines for Stable Ischemic Heart Disease in Primary Care (2000). *Ontario Program for Optimal Therapeutics*. Toronto: Queen's Printer of Ontario, pp. 10.

Guidelines on the management of stable angina pectoris. *Recommendations of the Task Force of the European Society of Cardiology*; 2006. p63.



Common Cold (Acute Rhinitis)



Common Cold Etiology

PRIMA

Paramyxoviruses
Rhinoviruses
Influenza viruses
Myxoviruses
Adenoviruses



Influenza vs. Colds: A Guide to Symptoms

Features	Flu	Cold
Onset of illness	Sudden	Slow
Fever	High fever	None
Exhaustion level	Severe	Mild
Cough	Dry severe or hacking	±
Throat	Fine	Sore
Nose	Dry and clear	Runny
Head	Achy	Headache-free
Appetite	Decreased	Normal
Muscles	Achy	Fine
Chills	Yes	No

Echinacea for Preventing and Treating the Common Cold

Cochrane Database of Systematic Reviews 2006; Issue 1

This systematic review of 16 trials assessed the effect of Echinacea in preventing and treating common colds. Trials compared preparations containing Echinacea with placebo, no treatment, or an alternative common cold treatment. Variations in preparations and quality of Echinacea made meta-analysis difficult, but in general, results suggested some preparations of Echinacea may be better than placebo.

Conclusions: Echinacea preparations vary widely. Some preparations with *E. purpurea* may be effective but results are inconsistent.

Definition

- viral upper respiratory tract infection (URTI) with inflammation

Epidemiology

- most common diagnosis in family medicine; peaks in winter months
- incidence: adults = 2-4/year, children = 6-10/year
- organisms
 - mainly rhinoviruses (30-35% of all colds)
 - others: coronavirus, adenovirus, RSV, influenza, parainfluenza, echovirus, coxsackie virus
- incubation: 1-5 days
- transmission: person-person contact via secretions on skin/objects and by aerosol droplets

Risk Factors

- psychological stress, excessive fatigue, allergic nasopharyngeal disorders, smoking, sick contacts

Clinical Features

- symptoms
 - local – nasal congestion, clear to mucopurulent secretions, sneezing, sore throat, conjunctivitis, cough
 - general – malaise, headache, myalgias, mild fever
- signs
 - boggy and erythematous nasal/oropharyngeal mucosa, enlarged lymph nodes
 - normal chest exam
- complications
 - secondary bacterial infection: otitis media, sinusitis, bronchitis, pneumonia
 - asthma/COPD exacerbation

Differential Diagnosis

- allergic rhinitis, pharyngitis, influenza, laryngitis, croup, sinusitis, bacterial infections

Management

- patient education
 - symptoms peak at 1-3 days and usually subside within 1 week
 - cough may persist for days to weeks after other symptoms disappear
 - no antibiotics indicated because of viral etiology
 - secondary bacterial infection can present within 3-10 days after onset of cold symptoms
- prevention
 - frequent hand washing, avoidance of hand to mucous membrane contact, use of surface disinfectant

- symptomatic relief
 - rest, hydration, gargling warm salt water, steam
 - analgesics and antipyretics: acetaminophen, ASA (not in children because risk of Reye's syndrome)
 - cough suppression: dextromethorphan or codeine if necessary
 - decongestants, antihistamines
 - zinc gluconate lozenge use is controversial
- patients with reactive airway disease will require increased use of bronchodilators and inhaled steroids

Zinc for the Common Cold

Cochrane Database of Systematic Reviews 2006; Issue 3; Last amendment: 1999

This systematic review of 7 randomized control trials investigated the effects of zinc lozenges for cold (acute upper respiratory tract infection) symptoms. Two trials suggested the lozenges were effective in reducing severity and duration of symptoms; overall, the lozenges did not appear to be effective.

Conclusions: The evidence for zinc lozenges treating the common cold is inconclusive, and there is a potential for side effects.

Contraception

- see Gynecology, GY18

Table 15. Methods of Contraception

	Advantages	Disadvantages
Combined OCP	Effectiveness: 99.9% with perfect use, 97-99% with typical use, cycle control, ↓ dysmenorrhea, ↓ menstrual flow, ↓ ovarian cancer, ↓ endometrial cancer, ↓ risk of fibroids, ↓ acne, ↓ hirsutism	Irregular bleeding, systemic hormonal side effects (breast tenderness, nausea, mood changes), no STI protection, slightly increased risk of venous thromboembolism (VTE), MI, and stroke, decreased quantity of breast milk postpartum
Progestin Only Pill (e.g. Micronor®)	At least 95% effective with perfect use, ↓ menstrual flow, ↓ cramping, no ↑ risk of VTE, MI or stroke, suitable for postpartum	Irregular bleeding, no STI protection, contraceptive reliability requires taking pill at the same time each day (within 3 hours), no pill free interval
Transdermal Patch (e.g. Evra®)	Same as OCP, easy to use, changed weekly, 99% effective with correct use	Same as OCP, skin irritation
NuvaRing® (inserted by patient)	Same as OCP, easy to use (in for 3 weeks, out for 1), less systemic hormonal side effects, 99% effective with correct use	Same as OCP, vaginitis, some women may be uncomfortable with self-insertion
DMPA IM progesterone injection q12 wks (e.g. DepoProvera®)	99.7% effective against pregnancy, infrequent dosing, ↓ menstrual flow or amenorrhea, ↓ risk of endometrial cancer	Irregular bleeding, delayed return of fertility, no STI protection, systemic hormonal side effects (most common is headache), weight gain, ↓ bone mineral density (check after 5 years)
Male Condom	97% effective against pregnancy and STIs when used properly. When used properly WITH spermicide they are close to 99.9% effective, no Rx required	Latex allergy, irritation, only effective before the expiry date, must be applied properly, can only be used once
Diaphragm	92-96% effective with perfect use, non-hormonal, female-controlled method of contraception, decreased risk of cervical cancer	Must be left in for 6h after intercourse, must be used with spermicide, incomplete STI protection, latex allergy, must be fitted by health care worker, increased risk of UTI, risk of toxic shock syndrome
Sponge	One-size-fits-all barrier method, does not require fitting by MD, available in pharmacies, 90% effective without a condom, 98% effective with a condom	Relatively expensive, only ~60% effective in parous women, incomplete STI protection, risk of toxic shock syndrome
Intrauterine Device (IUD)	99% effective against pregnancy, effective for 5 yrs, no daily regimen required, can be easily removed, ideal in post-partum women	No STI protection, increased relative risk of PID in first month, must be inserted by MD, risk of post-insertion vaso-vagal response, risk of uterine rupture is 0.6-1.6 per 1000, 2-10% expulsion rate
Levonorgestrel IUD (e.g. Mirena®)	↓ menstrual flow, less systemic hormonal side effects than OCP	Hormonal side effects (see <i>combined OCP</i>), expensive (~\$400)
Copper IUD (e.g. Nova T®)	↓ risk of endometrial cancer, less expensive (~\$170)	Irregular bleeding or ↑ menstrual flow, 6-20% women discontinue use in first 5 yrs because of pain or ↑ bleeding
Fertility Awareness/Natural Family Planning (e.g. symptothermal method)	Effectiveness: 95-98% with perfect use, 75-88% with typical use, increased awareness of gynecological health, reasonable for couples for whom an unplanned pregnancy would be acceptable	High probability of failure if not used consistently and correctly, no STI protection
Lactational amenorrhea	Very effective in breastfeeding women if menses not returned, fully or nearly fully breastfeeding baby and baby is under 6 months old	Not effective if infant receives any food supplementary to breastfeeding Must breastfeed regularly, even through the night (at least q6h)

Emergency Contraception (EC)

- hormonal EC (Yuzpe® or Plan B®, usually 2 doses taken 12 hrs apart) or post-coital IUD insertion
- hormonal EC is effective if taken within 72 hrs of unprotected intercourse (reduces chance of pregnancy by 75-85%), most effective if taken within 24 hrs, does not affect an established pregnancy
- post-coital IUDs inserted within 5 days of unprotected intercourse are significantly more effective than hormonal EC (reduces chance of pregnancy by ~99%)
- pregnancy test should be performed if no menstrual bleeding within 21 days of either treatment
- advance provision of hormonal emergency contraception increases the use of emergency contraception without decreasing the use of regular contraception
- pharmacists across Canada can now dispense Plan B® without a doctor's prescription (as of April 2005)



Absolute Contraindications to Combined OCP

- Known/suspected pregnancy
- Undiagnosed abnormal vaginal bleeding
- Thromboembolic disorders
- Cerebrovascular or coronary artery disease
- Estrogen dependent tumours (breast, uterus)
- Impaired liver function with acute liver disease
- Congenital hypertriglyceridemia
- Smoker >35 years old
- Migraines with focal neurological symptoms
- Uncontrolled hypertension

**Differential Diagnosis****Common Causes**

- Upper airway cough syndrome (postnasal drip)
- Asthma
- GERD
- Non-asthmatic eosinophilic bronchitis

Other Causes

- ACE inhibitors
- Aspiration
- Bronchiectasis
- Cystic fibrosis
- Chronic interstitial lung disease
- Lung/laryngeal cancer
- Pertussis
- Psychogenic
- Restrictive lung disease
- TB, atypical mycobacterium, and other chronic lung infections

Cough

History and Physical

- duration (chronic >3 months), onset, frequency, quality (dry vs. productive), sputum characteristics, provoking/relieving factors, recent changes
- associated symptoms: fever, dyspnea, hemoptysis, wheezing, chest pain, orthopnea, PND, rhinitis
- constitutional symptoms: fever, chills, fatigue, night sweats
- risk factors: smoking, occupation, exposure, family history of lung CA or other CA, TB status, recent travel
- medications (ACE inhibitors), allergies
- PMH: lung (asthma, COPD, CF), heart (CHF, MI, arrhythmias), chronic illness
- vitals including O₂ saturation, respiratory exam, HEENT and precordial exam

Investigations

- guided by findings on history and physical
 - consider throat swab, CXR, sputum culture, test for acid-fast bacilli
 - refer to respirology for PFTs as appropriate

Dementia

- see Psychiatry, PS18

Epidemiology

- 10% in patients over the age of 65, 25% in patients over the age of 85, 50% in patients over the age of 90
- prevalence increases with age, Down syndrome and head trauma
- differential diagnosis: Alzheimer's dementia, vascular dementia, Lewy-Body dementia, frontotemporal dementia

Investigations

- history, physical, MMSE
- investigations are completed to exclude reversible causes of dementia and should be selected based on the clinical circumstances
- CBC, liver, thyroid, renal function tests, serum electrolytes, serum glucose, vitamin B₁₂, folate, VDRL, HIV, SPECT, head CT, EEG

Management

- treat and prevent reversible causes
- provide orientation cues (e.g. calendars, clocks) and optimize vision and hearing
- family education, counselling and support (respite programs, group homes)
- pharmacologic therapy: NMDA receptor antagonists and cholinesterase inhibitors slow rate of cognitive decline; low-dose neuroleptics and anti-depressants can be used to treat behavioral and emotional symptoms
- 20% of patients develop clinical depression, most commonly seen in vascular dementia



Depression

- see Psychiatry, PS7

Etiology

- often presents as non-specific complaints (e.g. chronic fatigue, pain)
- depression is a clinical diagnosis and tests are done in order to rule out other causes of symptoms
- 2/3 of depressed persons may not receive appropriate treatment for their depression
- identification and early treatment improve outcomes

Screening Questions

- Are you depressed? (high specificity and sensitivity)
- Have you lost interest or pleasure in the things you usually like to do? (anhedonia)
- Do you have problems sleeping? (for those not willing to admit depression)

Assessment

- risk factors
- personal or family history of depression
- medications and potential substance abuse problems
- suicidality/homicidality
 - fill out Form 1 (in Ontario): application by physician to hospitalize a patient against his/her will for psychiatric assessment (up to 72 hours)

**Differential Diagnosis**

- Other psychiatric disorders (e.g. anxiety, personality, bipolar, schizoaffective, SAD, substance abuse/withdrawal)
- Early dementia
- Endocrine (hyper/hypothyroidism, DM)
- Liver failure, renal failure
- Chronic fatigue syndrome
- Vitamin deficiency (pernicious anemia, pellagra)
- Medication side effects (β-blockers, benzos)
- Infections (mononucleosis)
- Menopause
- Cancer (50% of patients with tumours, especially of brain, lung and pancreas, develop symptoms of depression before the diagnosis of cancer is made)

- functional impairment (e.g. work, relationships)
- at least 5 out of 9 criteria including anhedonia or depressed mood ≥ 2 weeks for actual diagnosis to be met (see sidebar)
- validated depression rating scales: Beck's depression inventory, Zung's self-rating depression scale, Children's depression inventory
- routine medical workup (physical examination, CBC, TSH, electrolytes, urinalysis, glucose, etc.)

Treatment

- goal: full remission of symptoms and return to baseline psychosocial function
- phases of treatment
 - acute phase (8-12 weeks): relieve symptoms and improve quality of life
 - maintenance phase (6-12 months after symptom resolution): prevent relapse/recurrence, must stress importance of continuing medication treatment for full duration to patients
- treatment can consist of pharmacotherapy alone or psychotherapy alone
- combination of antidepressant drug therapy and psychotherapy results in synergistic effects

Table 16. Common Medications

Class	Examples	Action	Side Effects	Notes
SSRI	paroxetine (Paxil®), fluoxetine (Prozac®), sertraline (Zoloft®), citalopram (Celexa®), fluvoxamine (Luvox®)	Block serotonin reuptake	Sexual dysfunction (impotence, decreased libido, delayed ejaculation, anorgasmia), headache, GI upset, weight loss, tremors, insomnia, fatigue	First line therapy for teens is fluoxetine; paroxetine is not recommended for teens (controversial)
SNRI	venlafaxine (Effexor®)	Block serotonin and NE reuptake	Insomnia, tremors, tachycardia, sweating	
SDRI	bupropion (Wellbutrin®)	Block dopamine and NE reuptake	Headache, insomnia, nightmares, seizures, less sexual dysfunction than SSRIs	
TCA	amitriptyline (Elavil®)	Block serotonin and NE reuptake	Sexual dysfunction, weight gain, tremors, tachycardia, sweating	Narrow therapeutic window, lethal in overdose

Prognosis

- up to 40% resolve spontaneously within 6-12 months
- risks of recurrence: 50% after 1 episode; 70% after 2 episodes; 90% after 3 episodes

Diabetes Mellitus (DM)

- see Endocrinology, E6

Epidemiology

- major health concern, affecting up to 10% of Canadians
- Type 1 Diabetes (DM1): 10-15% of DM, peak incidence age 10-15
- Type 2 Diabetes (DM2): 85-90% of DM, peak incidence age 50-55, up to 60,000 new cases in Canada per year
- gestational diabetes mellitus (GDM): 2-4% of all pregnancies
- incidence of Type 2 DM is rising dramatically as a result of an aging population, rising rates of obesity, and sedentary lifestyles
- leading cause of new-onset blindness and renal dysfunction
- Canadian adults with diabetes are twice as likely to die prematurely, compared to persons without diabetes

Risk Factors

- Type 1 DM
 - personal or family history of autoimmune disease
- Type 2 DM
 - first degree relative with DM
 - age ≥ 40 years
 - obesity (especially abdominal), hypertension, hyperlipidemia, coronary artery disease, vascular disease
 - prior GDM, macrosomic baby (>4 kg)
 - PCOS
 - history of IGT or IFG
 - presence of complications associated with diabetes
- both
 - member of a high risk population (e.g. Aboriginal, Hispanic, Asian or African descent)



Criteria for Depression

- M** Depressed Mood
- S** Increased/decreased Sleep
- I** Decreased Interest
- G** Guilt
- E** Decreased Energy
- C** Decreased Concentration
- A** Increased/decreased Appetite
- P** Psychomotor agitation/retardation
- S** Suicidal ideation



Must Ask About/Rule Out

- Bipolar/manic/hypomanic episodes
- Psychosis
- Anxiety
- Bereavement
- Substance use/abuse/withdrawal
- Suicidal/homicidal ideation

Common Antidepressants and Dosing

Drug	Starting Dose	Maximum Dose
citalopram (Celexa®)	20 mg PO OD	60 mg PO OD
escitalopram (Cipralex®)	10 mg PO OD	20 mg PO OD
fluoxetine (Prozac®)	20 mg PO q am	80 mg PO OD
paroxetine (Paxil®)	20 mg PO q am	50 mg PO OD
sertraline (Zoloft®)	50 mg PO OD	200 mg PO OD
fluvoxamine (Luvox®)	50 mg PO qhs	300 mg PO OD
venlafaxine (Effexor®)	75 mg PO OD	375 mg PO OD
(Effexor XR®)	37.5 mg PO OD	225 mg PO OD
bupropion (Wellbutrin®-immed)	100 mg PO bid	450 mg PO OD
(Sustained release)	100 mg PO qam	400 mg PO OD
amitriptyline (Elavil®)	25 mg PO qhs	300 mg PO OD
mirtazapine (Remeron®)	15 mg PO qhs	45 mg PO OD

Combined Pharmacotherapy and Psychological Treatment for Depression: A Systematic Review

Arch Gen Psychiatry 2004; 61(7):714-9

Study: Systematic review of randomized clinical trials.

Patients: 16 trials comprising 1842 patients.

Intervention: Antidepressant treatment alone vs. combination of psychological intervention and antidepressant therapy.

Main outcomes: Efficacy of and adherence to therapy.

Results: Overall, combined therapy was significantly more effective than antidepressant therapy alone (OR 1.86; 95% CI 1.38-2.52), however there was no difference in the rate of dropouts and non-responders in either treatment arm. In studies lasting >12 weeks, combined therapy showed a reduction in dropouts compared to non-responders (OR 0.59; 95% CI 0.39-0.88)

**DM Related Symptoms**

Hyperglycemia: polyphagia, polydipsia, polyuria, weight change, blurry vision, yeast infections

Diabetic ketoacidosis (DKA): fruity breath, anorexia, N/V, fatigue, abdo pain, Kussmaul breathing, dehydration

Hypoglycemia: hunger, anxiety, tremors, palpitations, sweating, headache, fatigue, confusion, seizures, coma



DKA can be triggered by infection, ischemia, infarction, intoxication, medication non-compliance.

**Long Term Complications of Diabetes**

- Microvascular: nephropathy, retinopathy, neuropathy
- Macrovascular: CAD, CVD, PVD

Diagnosis

- persistent hyperglycemia is the hallmark of all forms of diabetes

Table 17. Diagnosis of Insulin Associated Disorders

Condition	Diagnostic Criteria
Diabetes Mellitus	One of the following on 2 occasions: Random BG ≥ 11.1 mmol/L (200 mg/dL) with symptoms of DM (fatigue, polyuria, polydipsia, unexplained weight loss) OR Fasting BG ≥ 7.0 mmol/L (126 mg/dL) OR BG 2 hours post 75 g OGTT ≥ 11.1 mmol/L (200 mg/dL) OR HbA1c $\geq 6.5\%$
Impaired Fasting Glucose (IFG)	Fasting BG = 6.1-6.9 mmol/L (110-124 mg/dL)
Impaired Glucose Tolerance (IGT)	BG 2 hours post 75 g OGTT = 7.8-11.0 mmol/L (141-198 mg/dL)

Screening

- Type 2 DM
 - FBG in everyone ≥ 40 q3 yrs
 - more frequent and/or earlier testing if presence of ≥ 1 risk factor (as previously listed)
- GDM (see *Obstetrics*, OB13)
 - all pregnant women between 24-28 weeks gestation
 - non-fasting 1 hr 50 g OGCT ≥ 10.3 mmol/L (186 mg/dL) is diagnostic
 - if between 7.8-10.2 mmol/L (141-184 mg/dL), do confirmatory fasting 2 hr 75 g OGTT
 - if develop GDM, have a 50% chance of developing Type 2 DM over 20 years

Goals of Therapy**Table 18. Goals of Therapy in Diabetes Mellitus**

General	Avoid complications (e.g. ketoacidosis, hyperglycemia, infection) Prevent long-term complications (microvascular and macrovascular) Minimize negative sequelae associated with therapies (e.g. hypoglycemia, weight gain)
Fasting or Preprandial Glucose	Ideal: 4-7 mmol/L (72-126 mg/dL) Suboptimal: 7.1-10 mmol/L (128-180 mg/dL); action may be required Inadequate: > 10.0 mmol/L (180 mg/dL); action is required
HbA1c	≤ 0.07 or ≤ 0.065 in some type 2 DM patients at risk for nephropathy Suboptimal: 0.07-0.084 Inadequate: > 0.084
2 Hours Postprandial Glucose	5-10 mmol/L (90-180 mg/dL) if HbA1c target met 5-8 mmol/L (90-144 mg/dL) if HbA1c target not met
Blood Pressure	$< 130/80$ in adults (DM and HTN guidelines)
Lipids	LDL < 2.0 mmol/L (36 mg/dL) Triglycerides < 1.5 mmol/L (27 mg/dL) Total cholesterol/HDL ratio < 4.0 mmol/L (72 mg/dL)

Assessment and Monitoring**Table 19. Assessment and Monitoring**

	Initial Assessment	q2-4months	Annually
History	<ul style="list-style-type: none"> • Symptoms of hyperglycemia, ketoacidosis, hypoglycemia • Past medical history • Functional inquiry • Family history • Risk factors • Medications • Sexual function • Lifestyle 	<ul style="list-style-type: none"> • Diabetes-directed history • Screen for awareness and frequency of hypoglycemia and DKA • Glucose monitoring • Use of insulin and oral agents 	<ul style="list-style-type: none"> • Diabetes-directed history • Screen for awareness and frequency of hypoglycemia and DKA • Glucose monitoring • Use of insulin and oral agents • Sexual function • Lifestyle counselling • Psychosocial issues
Physical	<ul style="list-style-type: none"> • General: Ht, Wt, BMI, BP • Head and neck: fundoscopy, thyroid exam • Cardiovascular exam: signs of CHF, pulses, bruits • Abdominal exam (e.g. for organomegaly) • Hand/foot/skin exam • Neurological exam 	<ul style="list-style-type: none"> • Wt, BP, BMI, WC • Foot exam for sensation, ulcers, or infection 	<ul style="list-style-type: none"> • Complete neuro exam for peripheral neuropathy • Remainder of exam as per PHE

Table 19. Assessment and Monitoring (continued)

	Initial Assessment	q2-4months	Annually
Investigations	<ul style="list-style-type: none"> • FBG, HbA1c, fasting lipids, microalbumin:creatinine ratio • ECG 	<ul style="list-style-type: none"> • HbA1c q3 months • FBG as needed 	<ul style="list-style-type: none"> • Fasting lipid profile • Resting or exercise ECG if age > 35 • Dipstick analysis for gross proteinuria; if negative: annual microalbuminuria screening with random albumin:creatinine ratio for Type 2 and Type 1 (5 yrs post puberty) • If positive: 24-hr urine for endogenous creatinine clearance rate and microalbuminuria q6-12months
Management	<ul style="list-style-type: none"> • Nutritional and physical education • Consider referral to diabetes education program if available • Monitoring BG: explain methods and frequency • Medication counselling: oral hypoglycemics and/or insulin, method of administration, dosage adjustments • Ophthalmology consult <ul style="list-style-type: none"> • Type 1 within 5 yrs • Type 2 at diagnosis 	<ul style="list-style-type: none"> • Assess progress towards long-term complications • Adjust treatment plan if necessary 	<ul style="list-style-type: none"> • Calibrate home glucose monitor • Arrange ophthalmology follow-up annually for Type 1 and q2years for Type 2 • Influenza vaccination annually

Long-term Non-pharmacological Weight Loss Interventions for Adults with Prediabetes
Cochrane Database of Systematic Reviews 2005; Issue 2

A meta-analysis, using 9 studies comprising 5168 patients, investigated the effectiveness of diet control, physical activity, behavioural weight programs and weight control interventions in adults with prediabetes. The analysis was limited by heterogeneous patient populations, but when compared with usual care, weight loss was 2.8 kg and BMI decrease was 1.3 kg/m² at one year. Modest but non-significant improvements in glycemic control, BP and blood lipid concentrations were noted. Studies with a follow-up of 3-6 years showed a significant decrease in diabetes onset when compared with controls.

Dietary advice for Treatment of Type 2 DM in Adults
Cochrane Database of Systematic Reviews 2007; Issue 3

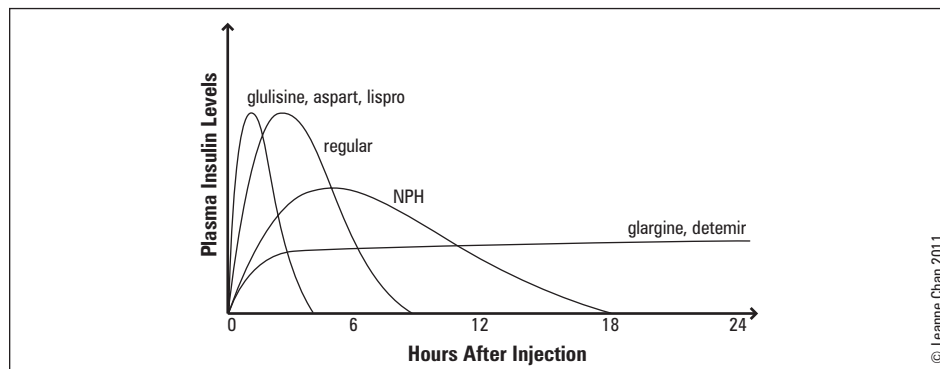
A meta-analysis, using 36 articles reporting a total of 18 trials following 1467 participants, showed that there is no high quality data on the efficacy of dietary treatment of type 2 diabetes. After 6 and 12 months, adoption of exercise improved glycated hemoglobin.

Nonpharmacologic Management

- diet
 - all diabetics should see a registered dietician
 - strive to attain healthy body weight
 - decrease combined saturated fats and trans-fatty acids to <10% of calories
 - avoid simple sugars, encourage complex carbohydrates, choose low glycemic-index foods
- physical activity and exercise
 - encourage 30-45 minutes of moderate exercise 4-7 days/week
 - promote cardiovascular fitness: increases insulin sensitivity, lowers BP and improves lipid profile
 - if insulin treated, may require alterations of diet, insulin regimen, injection sites and self-monitoring

Self-monitoring of Blood Glucose

- Type 1 DM: 3 or more self-tests/day is associated with a 1% reduction in HbA1c
- Type 2 DM: optimum frequency of self-tests remains unclear
- if FBG >14 mmol/L, perform ketone testing to rule out DKA
- if bedtime level is <7 mmol/L, have bedtime snack to reduce risk of nocturnal hypoglycemia

**Figure 6. Types of Insulin Preparation**

Calculate Total Insulin Required:

Type 1: 0.5-0.7 units/kg/day
 Type 2: 0.3 units/kg/day

Oral Hypoglycemics (DM2)

- available agents
 - biguanide: metformin (Glucophage®)
 - thiazolidinedione: troglitazone (Rezulin®), rosiglitazone (Avandia®)
 - alpha glucosidase inhibitor: acarbose (Precose®)
 - nonsulfonylureas: nateglinide (Starlix®), repaglinide (Gluconorm®)
 - sulfonylureas: glyburide (DiaBeta®), glimepiride (Amaryl®), gliclazide (Diamicon®)
 - DPP-4 inhibitor: sitagliptin (Januvia®)



Health Canada Recommendations on Management of Rosiglitazone Use in DM2

Rosiglitazone is indicated for:

- Use as monotherapy, in patients not controlled by diet and exercise alone
- For patients inadequately controlled on metformin or sulfonylurea, rosiglitazone should be added to, not substituted for, metformin or sulfonylurea
- In Canada, rosiglitazone is not approved for use:
 - with insulin therapy
 - with the combination of metformin AND sulfonylurea
 - in patients with pre-diabetes
- Contraindicated in patients with NYHA Class III and IV cardiac status
- Should be used with caution in any patient with NYHA Class I and II cardiac status
- Patients should be monitored for signs and symptoms of fluid retention, edema, and rapid weight gain
- Maximum daily dose used in combination with sulfonylurea should not exceed 4 mg

Metformin Monotherapy for Type 2 Diabetes Mellitus

Cochrane Database of Systematic Reviews 2005; Issue 3
 A Cochrane Review of 29 trials with 37 arms (5259 participants) compared metformin with sulfonylureas, placebo, diet, thiazolidinediones, insulin, meglitinides, and glucosidase inhibitors. The authors concluded that metformin may prevent some vascular complications and mortality in overweight and obese DM2 patients and as such may be considered first line therapy. There is no evidence that the studied alternative therapies have more benefit for glycaemia control, body weight, or lipids than does metformin.

Other Medications Used in DM

- ACE inhibitors for:
 - all hypertensive DM patients
 - elevated microalbuminuria (30-300 mg albumin in 24 h)
 - overt nephropathy (>300 mg albumin in urine in 24 h)
 - ARBs are second line for these conditions
- ASA for:
 - all diabetics, unless contraindicated
- statins
 - as required to attain target lipid profile

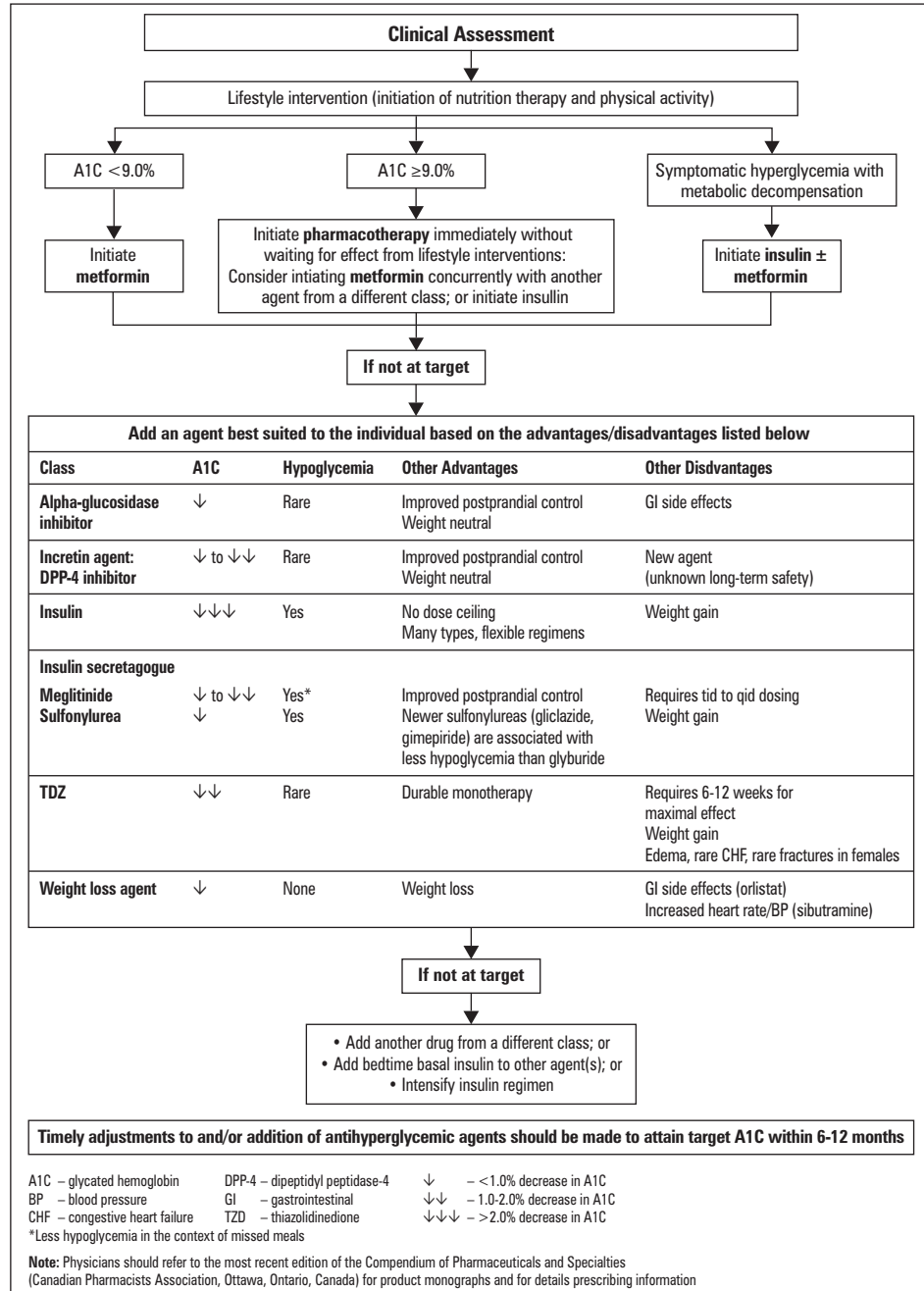


Figure 7. Management of Hyperglycemia in Type 2 Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2008; 32(suppl 1):S56 (used with permission).

Diarrhea

- see Gastroenterology, G14

Definition

- passage of frequent unformed stools (>200 g of stool/24 hours)
- can be acute (<14 days duration) or chronic (>14 days duration)

Etiology and Clinical Features

- acute diarrhea:
 - majority of cases are self-limiting
 - most commonly caused by viral infection (e.g. rotavirus)
 - fever and bloody stools increase probability of bacterial infection
 - consider *C. difficile* infection if recent hospitalization, recent antibiotic use, age >65, immunosuppression
- chronic diarrhea:
 - most commonly of non-infectious etiology
 - common causes include drugs (laxatives, antibiotics), infection (bacteria, parasites), inflammation (IBD, diverticulitis), neoplasia (colon cancer), malabsorption, maldigestion, IBS, and idiopathic

Treatment

- chronic diarrhea: nonspecific treatment often required before workup is complete
 - antidiarrheal opiates (e.g. loperamide) – most effective nonspecific treatment
 - ♦ should be used on a scheduled basis before meals rather than PRN
 - fibre (e.g. psyllium) – commonly used as adjunctive treatment
 - oral rehydration solution – offset electrolyte imbalances
 - lifestyle and diet changes

Dizziness

- see Otolaryngology, OT6

Epidemiology

- 70% see general practitioners initially; 4% referred to specialists
- frequency proportional to age; commonest complaint of ambulatory patients age >75

Differential Diagnosis

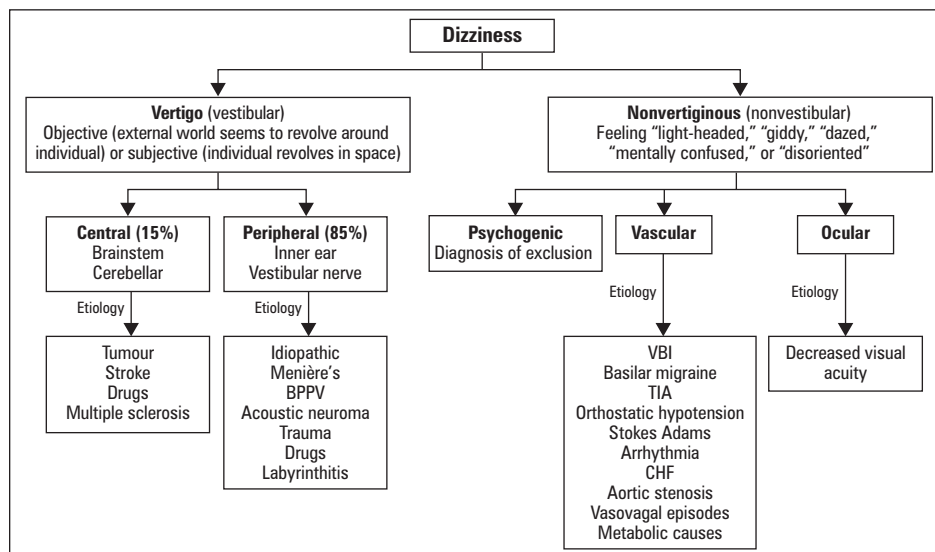


Figure 8. Differential Diagnosis of Dizziness

History

- clarify type of dizziness: vertigo, pre-syncope, dysequilibrium, light-headedness
- onset, precipitating/alleviating factors, preceding infections and activities, associated symptoms, previous experiences of dizziness
- duration (seconds to minutes vs. hours vs. days to weeks vs. persistent)
- exacerbations
 - worse with head movement or eye closure (vestibular)
 - no change with head movement and eye closure (nonvestibular)
 - worse with exercise (cardiac/pulmonary causes)

- associated symptoms
 - neurologic (central)
 - ♦ transient diplopia, dysphagia, dysarthria, ataxia (TIA, VBI, migraine)
 - ♦ persistent sensory and/or motor deficits (CNS)
 - audiologic (peripheral)
 - ♦ hearing loss, tinnitus, otalgia, aural fullness, recruitment
 - others
 - ♦ nausea, vomiting (peripheral vestibular disorders)
 - ♦ SOB, palpitations (hyperventilation, cardiac problem)
- general medical history
 - HTN, diabetes, heart disease, fainting spells, seizures, cerebrovascular disease, migraines
 - ototoxic drugs: aminoglycosides (gentamicin, streptomycin, tobramycin), erythromycin, ASA, antimalarials
 - hypotension (secondary to diuresis): furosemide, caffeine, alcohol



Dix-Hallpike Test

- Have the patient seated with legs extended and head at 45° rotation
- Rapidly shift patient to supine position with head fully supported in slight extension (for 45 seconds)
- Observe for rotatory nystagmus and ask about sensation of vertigo



Screening Instruments for Domestic Violence

A) WAST-SHORT

1. In general how would you describe your relationship?
 - a. Lot of tension
 - b. Some tension
 - c. No tension
2. Do you and your partner work out arguments with . . . ?
 - a. Great difficulty
 - b. Some difficulty
 - c. No difficulty

Endorsing either question 1 ("a lot of tension") or question 2 ("great difficulty") makes intimate partner violence exposure likely

B) HITS

- How often does your partner:
1. Physically Hurt you?
 2. Insult you?
 3. Threaten you with harm?
 4. Scream or curse at you?

Each question on HITS to be answered on a 5 point scale ranging from 1 (= never) to 5 (= frequently)
A total score of 10.5 is significant



How to Document Abuse

- Take photographs (with permission) of known or suspected injuries
- Use an injury location chart or "body map" when documenting physical findings
- Document any investigations ordered (e.g. x-ray)
- Write legibly or use a computer
- Record the patient's own words in quotation marks
- Avoid phrases that imply doubt about the patient's reliability (e.g. "patient claims that...")
- Record the patient's demeanor (e.g. upset, agitated)
- Record the time of day the patient is examined and how much time has elapsed since the abuse occurred

Physical Exam/Investigations

- syncopal
 - cardiac, peripheral vascular, and neurologic exams
 - bloodwork, ECG, 24-hr Holter, treadmill stress test, loop ECG, tilt table testing, carotid and vertebral doppler, EEG
- vertiginous
 - ENT and neurologic exams
 - Dix-Hallpike, consider audiometry and MRI if indicated
- non-syncopal, non-vertiginous
 - cardiac and neurologic exams
 - 3-minute hyperventilation trial, ECG, EEG

Treatment

- guided by history, physical and investigations
- include education, lifestyle modification, physical maneuvers (e.g. Epley for BPPV), symptomatic management (e.g. antiemetics), pharmacotherapy and surgery
- refer when significant central disease suspected, vertigo of peripheral origin is persistent (lasting >2-4 weeks), or if atypical presentation

Domestic Violence/Elder Abuse

INTIMATE PARTNER VIOLENCE

Definition

- includes physical, sexual, emotional, psychological and financial abuse (see Emergency Medicine, ER28)

Epidemiology

- lifetime prevalence of intimate partner violence against women is between 25% to 30%
- women who experience abuse have increased rates of injury, death and health consequences including 50-70% increase in gynecological, central nervous system, stress-related problems
- occurs in all socioeconomic, educational and cultural groups with increased incidence in pregnancy, disabled women, and 18-24 age group
- 25-50% chance of child abuse or neglect in families where abuse occurs
- physician recognition rates as low as 5%

Presentation

- multiple visits with vague, ill-defined complaints such as: headaches, gastrointestinal symptoms, insomnia, chronic pain, hyperventilation
- may also present with injuries inconsistent with history

Management

- screen ALL patients
 - always have a high index of suspicion
 - physician is often first person to get disclosure
 - health care visits are an important opportunity for physicians to address intimate partner violence
 - asking about abuse is the strongest predictor of disclosure
 - several screening tools (see sidebar) exist to identify victims of partner violence
 - make sure to determine the victim's level of immediate and long term danger and ask if there are weapons in the house

- ensure patient safety
 - victim most at risk for homicide when attempting to leave home or following separation
- provide community resources
 - safety planning includes ensuring that there is access to an exit in the home, establishing a safe place to go and having money, clothes, keys, medications, important documents and other emergency items prepared should the patient need to leave quickly
 - shelter or helpline number with legal advocacy and counselling services
 - involve social workers or domestic violence advocates
 - marital counselling inappropriate until safety is established and violence under control
- appointment for follow-up to assess whether condition is better or worse
- reassure patient she/he is not to blame and that the assault is a crime
 - goal is to convey the message that “As your doctor, I am concerned for your safety” and “Your partner has a problem that he/she needs help with” and “I want to help you”
 - reporting suspected or known child abuse is mandatory (see [Emergency Medicine](#), ER60)
 - spousal abuse is a criminal act, but not reportable without the woman's/man's permission
- DOCUMENT all evidence of abuse related visits for medico-legal purposes

ELDER ABUSE

Definition

- mistreatment of older people by those in a position of trust, power, or responsibility for their care
- types of abuse:
 - psychological (e.g. threatening, intimidating, insulting, demeaning, withholding information that may be important to them, ignoring)
 - financial (e.g. stealing, pressuring to sell or share home, misusing power of attorney)
 - physical (e.g. hitting, burning, locking in room, inappropriate use of physical restraints, withholding or misusing medication)
 - sexual
 - neglect



Risk Factors

- Female
- Older age (age 80 and older)
- Physical and mental frailty

Epidemiology

- 7% of adults in Canada age >65 reported experiences of emotional or financial abuse
- older adults who live with someone are more likely to be abused than those who live alone
- 2/3 of reported abuse cases involved family members, most often adult children followed by spouses
- older females are more likely to be abused than older males
- men are more likely than women to be victimized by an adult child (45% vs. 35%)
- women are more likely than men to experience violence at the hands of a spouse (30% vs. 19%) (Statistics Canada, 2004)
- reasons for under-reporting: fear, shame, cognitive impairment, language/cultural barriers, and social and geographic isolation

Screening

- insufficient evidence to include or exclude as part of the periodic health examination, but recommended that physicians be alert for indicators of abuse and institute measures to prevent further abuse
- general questions such as “Do you feel safe at home?” and move into more specific questions about different kinds of abuse

Presentation

- signs that an older adult is being abused may include:
 - depression, fear, anxiety, passivity, unexplained injuries, dehydration, malnutrition, poor hygiene, rashes, pressure sores, and over-sedation/inappropriate medication use

Management

- gather information from all sources (e.g. family members, health care providers, neighbours)
- perform a thorough physical examination
- ensure immediate safety and devise a plan for follow-up
- additional steps depend on whether the patient accepts intervention and whether they are capable of making decisions about their care
- interventions may include use of protective and legal services, senior resource nurses, elder abuse intervention teams and senior support groups

Dyspepsia

- see [Gastroenterology](#), G6

Definition and Clinical Features

- defined as epigastric pain or discomfort
- can be associated with fullness, belching, bloating, heartburn, food intolerance, nausea or vomiting

Epidemiology

- annual incidence 1-2%, prevalence 20-40%

Etiology

- common: functional, peptic ulcer disease, gastroesophageal reflux disease, gastritis
- others: cholelithiasis, irritable bowel disease, esophageal or gastric cancer, pancreatitis, pancreatic cancer, Zollinger-Ellison syndrome, and abdominal angina

History

- symptoms may not be useful in finding cause
- association with food, anorexia, nausea, vomiting, NSAID use
- symptoms suggestive of underlying pathology: weight loss, dysphagia, persistent vomiting, gastrointestinal bleeding (hematemesis, hematochezia)

Investigations and Management

- empiric therapy: H₂ receptor blockers, proton pump inhibitors
- testing for *H. pylori*: serology, urea breath test
- upper endoscopy (preferred), upper GI series

Dyspnea

- see [Respirology](#), R2 and [Emergency Medicine](#), ER27

History and Physical

- cough, sputum, hemoptysis, wheezing, chest pain, palpitations, dizziness, edema
- asthma, allergy, eczema, ASA/NSAID sensitivity, nasal polyps
- constitutional symptoms
- smoking, recreational drugs, medications
- occupational exposure, environmental exposure (e.g. pets, allergens, smoke)
- travel and birth place
- FHx of atopy
- previous CXR or PFTs
- exam: vitals, respiratory, precordial, HEENT, signs of anemia/liver failure/heart failure

Investigations

- CXR, ECG
- PFTs, ABG acutely if indicated

Management

- ABC's: send to Emergency Department if in severe respiratory distress
- depends on cause

Dysuria

- see [Urology](#), U4

Definition

- the sensation of pain, burning or discomfort on urination

Epidemiology

- in adulthood, more common in women than men
- approximately 25% of women report one episode of acute dysuria per year
- most common in women 25-54 years of age and in those who are sexually active
- in men, dysuria becomes more prevalent with increasing age

Etiology

- infectious
 - most common cause
 - presents as cystitis, urethritis, pyelonephritis, vaginitis or prostatitis
- non-infectious
 - hormonal conditions (postmenopausal hypoestrogenism), obstruction (BPH, urethral strictures), neoplasms, allergic reactions, chemicals, foreign bodies, trauma



DDX of Dyspnea

- Pulmonary embolism
- Deconditioning
- Foreign body aspiration
- DKA
- Anemia
- Asthma
- Pneumothorax



Risk Factors for Complicated Urinary Tract Infection

- Male sex
- Pregnancy
- Recent urinary tract instrumentation
- Functional or anatomic abnormality of the urinary tract
- Chronic renal disease
- Diabetes
- Immunosuppression
- Indwelling catheter

Table 20. Etiology, Signs and Symptoms of Dysuria

Infection	Etiology	Signs and Symptoms
UTI/Cystitis	<i>E. coli</i> , <i>S. saprophyticus</i> , <i>Proteus mirabilis</i> , <i>Enterobacter</i> , <i>Klebsiella</i> , <i>Pseudomonas</i>	Internal dysuria throughout micturition, frequency, urgency, incontinence, hematuria, nocturia, back pain, suprapubic discomfort, low grade fever (rare)
Urethritis	<i>C. trachomatis</i> , <i>N. gonorrhea</i> , <i>Trichomonas</i> , <i>Candida</i> , herpes	Initial dysuria, urethral/vaginal discharge, history of STI
Vaginitis	<i>Candida</i> , <i>Gardnerella</i> , <i>Trichomonas</i> , <i>C. trachomatis</i> , atrophic, herpes, lichen sclerosis	External dysuria/pain, vaginal discharge, irritation, dyspareunia, abnormal vaginal bleeding
Prostatitis	<i>E. coli</i> , <i>C. trachomatis</i> , <i>S. saprophyticus</i> , <i>Proteus mirabilis</i> , <i>Enterobacter</i> , <i>Klebsiella</i> , <i>Pseudomonas</i>	Dysuria, fever, chills, urgency, frequency, tender prostate
Pyelonephritis	<i>E. coli</i> , <i>S. saprophyticus</i> , <i>Proteus mirabilis</i> , <i>Enterobacter</i> , <i>Klebsiella</i> , <i>Pseudomonas</i>	Internal dysuria, fever, chills, flank pain radiating to groin, CVA tenderness, nausea or vomiting

Investigations

- no investigations necessary when history and physical consistent with uncomplicated UTI – treat empirically (urinalysis can be performed when indicated by dipstick or microscopy)
- radiologic studies and other diagnostic tests if atypical presentation
- urinalysis/urine R&M: pyuria, bacteriuria, hematuria
- urine C&S
- if vaginal/urethral discharge present: wet mount, Gram stain, KOH test, vaginal pH, culture for yeast and *Trichomonas*
- endocervical or urethral swab for *N. gonorrhea* and *C. trachomatis*
- renal U/S ± voiding cystourethrogram (VCUG) in children with recurrent UTI

Management

- UTI/cystitis
 - pregnant women with bacteriuria (2-7%) must be treated even if asymptomatic, due to risk of preterm labour; need to follow with monthly urine cultures and retreat if still infected
 - patients with recurrent UTIs (>3 per year), should be considered for prophylactic antibiotics
 - if complicated UTI, patients require longer courses of broader spectrum antibiotics
- urethritis
 - when swab is positive for chlamydia or gonorrhea must report to Public Health
 - all patients should return 4-7 days after completion of therapy for clinical evaluation

Does this Woman have an Acute Uncomplicated Urinary Tract Infection?

JAMA 2002; 287:2701-2710

Purpose: To review the accuracy and precision of history taking and physical examination for diagnosing UTI in women.

Study Characteristics: Systematic review of 9 studies looking at the accuracy or precision of history or physical examination in diagnosing uncomplicated UTI.

Participants: Healthy women. Infants, children or adolescents, pregnant women, nursing home patients, and patients with complicated UTI were excluded.

Main Outcomes: Precision and accuracy of history taking and physical exam.

Results: No studies examined precision as an outcome. Four symptoms and one sign significantly increased the probability of UTI: dysuria, frequency, hematuria, back pain, and CVA tenderness. Four symptoms and one sign significantly decreased the probability of UTI: absence of dysuria, absence of back pain, a history of vaginal discharge, a history of vaginal irritation, and vaginal discharge on examination.

Conclusions: Women who present with 1 or more symptoms of UTI have a probability of infection approaching 50%, effectively ruling in infection. Additional historical elements, physical examination, and urinalysis is unable to lower the post-test probability of UTI to a level where it can be ruled out. Additional testing, such as culture, should be pursued.



Prevention of UTIs

- Maintain good hydration (especially with cranberry juice)
- Wipe urethra from front to back to avoid contamination of the urethra with feces from the rectum
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse

Epistaxis

- see Otolaryngology, OT27

Table 21. Characteristics of Anterior vs. Posterior Bleeds

	Anterior (90%)	Posterior (10%)
Location/ Origin	Little's Area/Kiesselbach's Plexus	Woodruff's Plexus/Sphenopalatine Artery
Age	2-10, 50-80	Usually >50
Common Cause	Trauma (digital, fracture, foreign body), dry air, cool climate, post URTI, nasal dryness, chemical (nasal sprays, cocaine), tumour	Systemic: hepatic disease, primary/secondary bleeding disorder, medications (ASA, NSAIDs, warfarin), HTN, atherosclerosis
Treatment	Conservative: <ul style="list-style-type: none"> Position: upright leaning forward with direct digital pressure over soft part of nostril for >10 min ("pinch" up to cartilage) Humidifier in bedroom, nasal saline sprays, bacitracin or Vaseline® application to Little's area Silver nitrate Gelfoam/Hemostat Nasal packing with Vaseline® gauze, nasal catheter or sponge Cotton soaked in vasoconstrictor (oxymetazoline 0.5%) and topical anesthetic (4% lidocaine) placed in anterior nasal cavity with direct pressure for >10 min Investigations: CBC, Hct, cross & type, INR, PTT (only if severe), CT/nasopharyngoscopy if suspected tumour 	Emergency: ENT/ER consult for posterior packing with an intranasal balloon/Foley catheter Embolization/surgery
Prognosis	Usually stops with >10 min of pressure to nose	Copious bleed, often swallowed and vomited May lead to hypovolemic shock if not treated promptly

Erectile Dysfunction (ED)

- see Urology, U30

Definition

- consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual performance of ≥ 3 months duration

Epidemiology

- ~20% of men aged 40; ~50% of men aged 70

Etiology

- organic: vascular (90%) (arterial insufficiency, atherosclerosis), endocrine (low testosterone, diabetes), anatomic (structural abnormality e.g. Peyronie's), neurologic (post-op, DM), medications (clonidine, antihypertensives, psychotropics)
- psychogenic (10%)

Table 22. Differentiation Between Organic and Psychogenic Erectile Dysfunction

Characteristic	Organic	Psychogenic
Onset	Gradual	Acute
Circumstances	Global	Situational
Course	Constant	Varying
Non-coital erection	Poor	Rigid
Psychosexual problem	Secondary	Long history
Partner problem	Secondary	At onset
Anxiety and fear	Secondary	Primary

Walsh: Campbell's Urology, 8th ed. Table 46-4.

History

- comprehensive sexual, medical and psychosocial history
- time course
 - last satisfactory erection
 - gradual or sudden onset
 - attempts at sexual activity
- quantify
 - presence of morning or night time erections
 - stiffness (scale of 1-10)
 - ability to initiate and maintain an erection with sexual stimulation
 - erection stiffness during sex (scale of 1-10)
- qualify
 - partner or situation specific
 - loss of erection before penetration or climax
 - degree of concentration required to maintain an erection
 - percentage of sexual attempts satisfactory to patient and/or his partner
 - significant bends in penis or pain with erection
 - difficulty with specific positions
 - impact on quality of life and relationship

Investigations

- hypothalamic-pituitary-gonadal axis evaluation: testosterone (free + total), prolactin, LH
- risk factor evaluation: fasting glucose, HbA1c, lipid profile
- others: TSH, CBC, urinalysis
- specialized testing
 - psychological and/or psychiatric consultation
 - in-depth psychosexual and relationship evaluation
 - nocturnal penile tumescence and rigidity (NPTR) assessment
 - vascular diagnostics (e.g. doppler studies, angiography)

Management

Table 23. Management of Erectile Dysfunction

Nonpharmacologic	Pharmacologic	Surgical
Lifestyle changes (alcohol, smoking, exercise)	Oral agents	Implants
Relationship/sexual counselling	Suppository (MUSE: male urethral suppository for erection)	Vascular repair
Vacuum devices	Injections	Realignment

Modifiable Risk Factors and Erectile

Dysfunction: Can Lifestyle Changes Modify Risk?
Urology 2000; 56:302-306

Study: A prospective cohort study designed to examine whether changes in smoking, heavy alcohol consumption, sedentary lifestyle, and obesity are associated with the risk of ED in men aged 40-70.

Results: Obesity was associated with ED ($P=0.006$), with baseline obesity conferring higher risk regardless of subsequent weight loss. Level of physical activity was associated with ED ($P=0.01$): those initiating physical activity or remaining active had a lower risk of ED, while those who remained sedentary had a higher risk. As compared to their sedentary peers, those who initiated exercise in midlife had a 70% reduced ED rate. Changes in smoking or alcohol intake were not associated with ED ($P>0.3$).

Conclusion: Although making lifestyle changes in midlife may be too late to reverse the effects of smoking, obesity, and alcohol consumption on ED, initiating physical activity in midlife may in fact reduce ED relative to peers who remain sedentary. Adopting a healthy lifestyle early in life may be the best approach to reducing the risk of developing ED in later years.

- pharmacologic treatment
 - phosphodiesterase type 5 inhibitors (see Table 24)
 - alpha adrenergic blockers (e.g. yohimbine)
 - serotonin antagonist and reuptake inhibitor (e.g. trazodone)
 - testosterone – currently only indicated in patients presenting with hypogonadism and testosterone deficiency (note: breast/prostate cancer are absolute contraindications)

Table 24. Phosphodiesterase Type 5 Inhibitors

Examples	Dosing (1 dose/day)	Specifics	Side Effects	Contraindications
sildenafil (Viagra®)	25-100 mg/dose	Take 0.5-4 hr prior to intercourse May last 24 hours	Flushing, headache, indigestion	Not to be used in patients taking nitrates
tadalafil (Cialis®)	5-20 mg/dose	Effects may last 36 hours	As above	As above
varafenafil (Levitra®)	2.5-20 mg/dose	Take 1 hr prior to intercourse	As above	As above

Fatigue

Epidemiology

- 25% of office visits to family physicians
 - peaks in ages 20-40
 - women 3-4x > men
- 50% have associated psychological complaints/problems, especially if <6 month duration

Differential Diagnosis

Table 25. Differential Diagnosis of Fatigue: PS VINDICATE

P	Psychogenic	Depression, sleep disorder, life stresses , anxiety disorder, chronic fatigue syndrome, fibromyalgia
S	Sedentary	Unhealthy/sedentary lifestyle
V	Vascular	Stroke
I	Infectious	Viral (e.g. mononucleosis, hepatitis), bacterial (e.g. TB), fungal, parasitic, HIV
N	Neoplastic	Any malignancy
	Nutrition	Anemia (Fe deficiency, B ₁₂ deficiency)
	Neurogenic	Myasthenia gravis, multiple sclerosis, Parkinson's Disease
D	Drugs	Beta-blockers, antihistamines, anticholinergics, benzodiazepines, antiepileptics
I	Idiopathic	
C	Chronic illnesses	CHF, lung diseases (e.g. COPD, sarcoidosis), renal failure, chronic liver disease
A	Autoimmune	SLE, RA, mixed connective tissue disease, polymyalgia rheumatica
T	Toxin	Substance abuse (e.g. alcohol), heavy metal
E	Endocrine	Hypothyroidism, diabetes , Cushing's syndrome, adrenal insufficiency, pregnancy

Common causes are in **bold**.

Investigations

- psychosocial causes are common, so usually minimal investigation is warranted
- physical causes of fatigue usually have associated symptoms/signs that can be elicited from a focused history and physical examination
- investigations should be guided by history and physical and may include:
 - CBC + differential, electrolytes, BUN, Cr, ESR, glucose, TSH, ferritin, vit B₁₂, total protein, albumin, AST, ALT, ALP, bilirubin, calcium, phosphate, ANA, beta-hCG
 - urinalysis, CXR, ECG
 - additional tests: serologies (Lyme disease, hepatitis B and C screen, HIV, ANA) and PPD skin tests

Treatment

- treat the cause
- if etiology undetermined (underlying cause cannot be identified in 1/3 of patients)
 - reassurance and follow-up, especially with fatigue of psychogenic etiology
 - supportive counselling, behavioural, or group therapy
 - encourage patient to stay physically active to maximize function
 - review all medications, OTC, and herbal remedies for drug-drug interactions and side effects
 - prognosis: after 1 year, 40% are no longer fatigued



Fatigue Red Flags

Fever
Weight loss
Night sweats
Neurological deficits
Ill-appearing

CHRONIC FATIGUE SYNDROME (CFS)

Definition (CDC 2006) – must meet both criteria

1. new or definite onset of unexplained, clinically evaluated, persistent or relapsing chronic fatigue, not relieved by rest, which results in occupational, educational, social, or personal dysfunction
 2. concurrent presence of at least 4 of the following symptoms for a minimum of 6 months:
 - impairment of short-term memory or concentration, severe enough to cause significant decline in function
 - sore throat
 - tender cervical or axillary lymph nodes
 - muscle pain
 - multi-joint pain with no swelling or redness
 - new headache
 - unrefreshing sleep
 - post-exertion malaise lasting >24 hours
- exclusion criteria: medical conditions that may explain the fatigue, certain psychiatric disorders (depression with psychotic or melancholic features, schizophrenia, eating disorders), substance abuse, severe obesity (BMI >45)

Exercise Therapy for Chronic Fatigue

Cochrane Depression, Anxiety, and Neurosis Group.
Cochrane Database of Systematic Reviews 2004;
Issue 3

Purpose: To determine the effectiveness of exercise therapy for Chronic Fatigue Syndrome (CFS).

Methods: Systematic review of 5 RCTs with 336 patients of all ages with a clinical diagnosis of CFS.

Interventions: Exercise therapy alone was compared with treatment as usual (or relaxation and flexibility), pharmacotherapy (fluoxetine), or exercise therapy combined with either pharmacotherapy or patient education.

Results: At 12 weeks, patients undergoing exercise therapy were less fatigued than controls (SMD -0.77; 95% CI, -1.26 to -0.28). Physical functioning was also significantly improved, but there were more dropouts with exercise therapy. Compared with fluoxetine, patients receiving exercise therapy were less fatigued (WMD -1.24; 95% CI, -5.31 to 2.83). Patients receiving combination therapy with exercise therapy and either fluoxetine or patient education, did better than those on monotherapy.

Conclusions: Patients may benefit from exercise therapy. Combination therapy with either fluoxetine or education may offer additional benefit. Further high quality trials are needed.

Epidemiology

- F>>M, Caucasians > other groups, majority in their 30s
- CFS found in <5% of patients presenting with fatigue

Etiology

- unknown, likely multifactorial
- may include infectious agents, immunological factors, neurohormonal factors, and/or nutritional deficiency

Investigations

- no specific laboratory tests diagnose CFS

Treatment

- promote sleep hygiene
- provide support and reassurance that most patients improve over time
- non-pharmacological
 - regular physical activity
 - optimal diet
 - psychotherapy (e.g. CBT), family therapy, support groups
- pharmacological
 - to relieve symptoms: e.g. antidepressants, anxiolytics, NSAIDs, antimicrobials, antiallergy therapy, antihypertensive therapy (increase dietary sodium, fludrocortisone)

Fever

Differential Diagnosis

Table 26. Differential Diagnosis of Fever

Infection	Cancer	Medications		Other
Bacterial	Leukemia	Allopurinol	Nifedipine	Irritable Bowel Disease
Viral	Lymphoma	Captopril	Phenytoin	Collagen-vascular disease
TB	Other Malignancies	Cimetidine	Diuretics	DVT
		Heparin	Barbiturates	
		INH	Antihistamines	
		Meperidine		

Definition

- mean oral temperature = 36.8°C, unadjusted TM temperature is 0.4°C lower, rectal temperature usually 0.4°C higher
- diurnal variation: usually 0.5°C higher at 4PM vs. 6AM
- fever = oral temperature >37.2°C (AM), 37.7°C (PM)

History

- fever
 - peak temperature, thermometer, route
 - time of day
 - response to antipyretics
- systemic symptoms
 - weight loss, fatigue, rash, arthralgia

- symptoms of possible source
 - UTI/pyelonephritis: dysuria, foul-smelling urine, incontinence, frequency, hematuria, flank pain
 - pneumonia: cough, pleuritic chest pain
 - URTI: cough, coryza, ear pain
 - meningitis: headache, confusion, stiff neck, rash
 - osteomyelitis: bone pain
 - skin: purulent discharge
 - PID: discharge, dyspareunia
 - gastroenteritis: abdominal pain, diarrhea, blood per rectum, vomit
 - medications
 - DVT: swollen legs, pain in calf, shortness of breath, pleuritic chest pain
 - history of cancer/family history of cancer
- infectious contacts
 - travel history, camping, daycare, contact with TB, foodborne, animals

Investigations

- CBC & differential, blood culture, urine culture, urinalysis
- stool O&P, Gram stain, culture
- CXR, TB skin test, sputum culture
- LP

Management

- general: sponge bath, light clothing
- acetaminophen/ibuprofen as needed
- treat underlying cause

Joint Pain

- see [Rheumatology](#), RH3

Differential Diagnosis

Table 27. Differential Diagnosis of Joint Pain

Non-Articular		Articular	
Localized	Generalized	Inflammatory	Degenerative
Bursitis Tendonitis Capsulitis	Fibromyalgia Polymyalgia rheumatica	Seropositive <ul style="list-style-type: none"> • Rheumatoid arthritis • Systemic lupus erythematosus • Scleroderma • Polymyositis • Sjogren's syndrome Seronegative <ul style="list-style-type: none"> • Ankylosing spondylitis • Inflammatory bowel disease • Psoriatic arthritis • Reactive arthritis Crystal <ul style="list-style-type: none"> • Gout • Pseudogout • Milwaukee shoulder, calcific periarthritis Infectious <ul style="list-style-type: none"> • Gonococcal • Non-gonococcal 	Primary <ul style="list-style-type: none"> • Familial Heberden's node • Inflammatory osteoarthritis • Regional hip or knee Secondary <ul style="list-style-type: none"> • Metabolic • Hemophiliac • Neuropathic • Traumatic

History

- number of joints involved – monoarticular, oligoarticular, polyarticular
- pattern of joints involved – symmetrical vs. asymmetrical, large vs. small joints, axial skeleton
- relation to activity (inflammatory better with activity, degenerative worse)
- relation to rest (inflammatory worse with rest, degenerative better)
- morning stiffness >30 minutes (inflammatory)
- soft tissue swelling, erythema (inflammatory)
- onset – acute vs. chronic (>6 weeks)
- trauma, infection, medications (steroids, diuretics)
- FHx of arthritis
- co-morbidities: diabetes mellitus (carpal tunnel syndrome), renal insufficiency (gout), psoriasis (psoriatic arthritis), myeloma (low back pain), osteoporosis (fracture), obesity (OA)
- constitutional symptoms (neoplasm)

- systemic features
 - fever (SLE, infection)
 - rash (SLE, psoriatic arthritis)
 - nail abnormalities (psoriatic, reactive arthritis)
 - myalgias (fibromyalgia, myopathy)
 - weakness (polymyositis, neuropathy)
 - GI symptoms (scleroderma, IBD)
 - GU symptoms (reactive arthritis, gonococemia)

Physical Exam

- vitals
- specific joint exams
- systemic features (skin, nails, eyes, hands)

Investigations

- CBC + differential, ESR, CRP, RF, ANA, HLA-B27, serum uric acid, calcium
- urinalysis
- tissue cultures
- x-ray
- joint aspirate for cell count + differential, culture, Gram stain, microscopy

Headache

- see [Neurology](#), N39

Primary Headaches

Table 28. Primary Headaches

	Migraine	Tension-type	Cluster	Caffeine Withdrawal
Epidemiology	12% of adults F>M 20% with aura 80% without aura	38% of adults, can be episodic or chronic	<0.1% of adults, M>>F	~50% of people drinking >2.5 cups/d
Duration	5-72 hrs	May occur as isolated incident or daily, duration is variable	<3 hrs at same time of day	Begins 12-24 hrs after last caffeine intake, can last ~1 wk
Pain	Classically unilateral and pulsatile, but 40% are bilateral, moderate-severe intensity, nausea/vomiting, photo/phonophobia	Mild to moderate pain, bilateral, fronto-occipital or generalized pain, band-like pain, ± contracted neck/scalp muscles, associated with little disability	Sudden, unilateral, severe, usually centered around eye, frequently awakens patient	Severe, throbbing, associated with drowsiness, anxiety, muscle stiffness, nausea, waves of hot or cold sensations
Triggers	Numerous (e.g. food, sleep disturbance, stress, hormonal, fatigue, weather, high altitude) Aggravated by physical activity	Stressful events, NOT aggravated by physical activity	Often alcohol	Discontinuing caffeine
Treatment of Acute Headache	1 st line: acetaminophen, ASA, ± caffeine 2 nd line: NSAIDs 3 rd line: 5HT agonists ± antiemetic	Rest and relaxation NSAIDs	Sumatriptan Dihydroergotamine High-flow O ₂ Intranasal lidocaine	Caffeine Acetaminophen or ASA ± caffeine
Prophylactic Therapy	1 st line: beta-blockers 2 nd line: TCAs 3 rd line: anticonvulsants	Rest and relaxation, physical activity, biofeedback	Lithium carbonate, prednisone, methysergide	Cut down on caffeine

Headache Red Flags

Sudden onset of severe headache
Worst headache ever
New headache after age 50
Headache present on awakening
Impaired mental status
Fever
Neck stiffness
Seizures
Focal neurologic deficits
Jaw claudication
Scalp tenderness
Worse with exercise, sexual activity orValsalva

Secondary Headaches

- caused by underlying organic disease
- account for <10% of all headaches, may be life-threatening
- etiology
 - space-occupying lesion
 - systemic infection (meningitis, encephalitis)
 - stroke
 - subarachnoid hemorrhage
 - systemic disorders (thyroid disease, hypertension, pheochromocytoma, etc.)
 - temporal arteritis
 - traumatic head injuries
 - TMJ or C-spine pathology
 - serious ophthalmological and otolaryngological causes of headache

- treatment
 - based on underlying disorder
 - analgesics may provide symptomatic relief

Investigations

- indicated only when red flags are present and may include:
 - CBC for suspected systemic or intracranial infection
 - ESR for suspected temporal arteritis
 - neuroimaging (CT or MRI) to rule out intracranial pathology
 - CSF analysis for suspected hemorrhage, infection, tumour or disorders related to CSF

Hearing Impairment



- see Otolaryngology, OT9

Definition

- hearing impairment: a raised hearing threshold measured as decibels of hearing loss relative to the normal population at specific frequencies
- hearing disability: hearing impairment that interferes with performing daily tasks

Epidemiology

- 10% of the population is hard of hearing or deaf
- 90% of age-related hearing loss (presbycusis) is sensorineural
- hearing loss detectable by audiology is present in greater than 1/3 of people over 65
- associated with significant physical, functional and mental health consequences

Classification

- conductive (sound does not reach cochlea)
- sensorineural (sound is not converted or transmitted via neural signals)
- mixed

Assessment

- infants
 - universal newborn hearing screening program
- elderly
 - whispered-voice test
 - ♦ whisper six test words 6 inches to 2 feet away from the patient's ear out of the visual field, ask patient to repeat the words (with non-test ear distraction)
 - tuning fork test
 - ♦ Rinne and Weber (not for general screening)
 - audioscope
 - ♦ delivers pure tone frequencies to obtain thresholds for frequencies of 250-8000 Hz

Management

- counsel about noise control and hearing protection programs (grade A evidence)
- refer patients with hearing loss for a complete audiological examination
- hearing amplification (e.g. hearing aids), assistive listening devices, and cochlear implants can dramatically improve quality of life

Does this Patient have Hearing Impairment?

JAMA 2006; 295:416-428

Purpose: To evaluate bedside clinical maneuvers used to evaluate the presence of hearing impairment.

Study: Evidence-based review of studies examining the accuracy or precision of screening questions and tests. 24 studies were included in this analysis.

Conclusions: Elderly patients who admit to having hearing impairment should be offered audiometry, while those who do not should undergo a whispered-voice test. Those who hear the whispered voice require no further testing, while those who do not require audiometry. The Weber and Rinne tests are not useful in screening for hearing impairment.

Hypertension

Epidemiology

- 20-25% of Canadian adults have HTN (and up to 50% undiagnosed)
- 16% have adequate BP control
- approximately 50% of adult Canadians are hypertensive by age 60
- 3rd leading risk factor associated with death
 - risk factor for CAD, CHF, cerebrovascular disease, renal failure, peripheral vascular disease

Definition

- hypertension
 - BP $\geq 140/90$ mmHg (see Figure 9)
- isolated systolic hypertension
 - sBP ≥ 140 and dBP < 90
 - associated with progressive reduction in vascular compliance
 - usually begins in 5th decade; up to 11% of 75 year olds



Symptoms of hypertension are usually **NOT PRESENT** (this is why it is called the "silent killer").

May have occipital headache upon awakening or organ specific complaints if advanced disease.



Hypertensive Emergencies

1. Accelerated malignant HTN with papilledema

2. Cerebrovascular:

Hypertensive encephalopathy
CVA with severe hypertension
Intracerebral hemorrhage
SAH

3. Cardiac:

Acute aortic dissection
Acute refractory LV failure
Acute MI with persistent ischemic pain after CABG

4. Renal:

Acute glomerulonephritis
Renal crises from collagen vascular diseases
Severe hypertension following renal transplantation

5. Excessive circulating catecholamines:

Pheochromocytoma
Tyramine containing foods or drug interactions with MAOIs
Sympathomimetic drug use (e.g. cocaine)
Rebound HTN after cessation of anti-hypertensive drugs (e.g. clonidine)

6. Eclampsia

7. Surgical:

Severe HTN prior to emergent surgery
Severe post-op HTN
Post-op bleeding from vascular suture lines

8. HTN following severe burns

9. Severe epistaxis

- accelerated hypertension
 - significant recent increase in BP over previous hypertensive levels associated with evidence of vascular damage on fundoscopy but without papilledema
- malignant hypertension
 - sufficient elevation in BP to cause papilledema and other manifestations of vascular damage (retinal hemorrhages, bulging discs, mental status changes, increasing creatinine)
 - not defined by absolute level of BP, but often requires BP of >200/140
 - develops in about 1% of hypertensive patients
- hypertensive urgency
 - sBP >210 or dBP >120 with minimal or no target-organ damage
- hypertensive emergency
 - high BP + acute target-organ damage

Etiology

- essential (primary) hypertension (>90%)
 - undetermined cause
- secondary hypertension (10%)
- watch for labile, “white coat” hypertension (office-induced elevated BP)

Predisposing Factors

- family history
- obesity (especially abdominal)
- alcohol consumption
- stress
- sedentary lifestyle
- smoking
- male gender
- age >30
- excessive salt intake/fatty diet
- African American ancestry
- dyslipidemia



Causes of Secondary Hypertension

ABCDE

Apnea, Aldosteronism
Bruits, Bad kidneys
Coarctation, Cushing's, Catecholamines,
Calcemia
Drugs
Endocrine disease

Table 29. Causes of Secondary Hypertension

Obstructive Sleep Apnea	Common cause		
Renal	Renovascular HTN Renal parenchymal disease, glomerulonephritis, pyelonephritis, polycystic kidney		
Endocrine	1° hyperaldosteronism Pheochromocytoma Cushing's syndrome Hyperthyroidism/hyperparathyroidism Hypercalcemia of any cause		
Vascular	Coarctation of the aorta Renal artery stenosis		
Drug-induced	Estrogens MAOIs Cocaine	Steroids Lithium Amphetamines	NSAIDs Decongestants Alcohol

Investigations

- for all patients with hypertension (D)
 - CBC, electrolytes, Cr, fasting glucose and lipid profile, 12-lead ECG, urinalysis
- for specific patient subgroups (D)
 - DM or renal disease: urinary protein excretion
 - increasing Cr OR history of renal disease or proteinuria OR HTN resistant to 3 meds OR presence of abdominal bruit: renal ultrasound, captopril renal scan, MRA/CTA (B)
 - if suspected endocrine cause: plasma aldosterone, plasma renin (D)
 - if suspected pheochromocytoma: 24h urine for metanephrines and creatinine (C)
 - echocardiogram for left ventricular dysfunction assessment if indicated (C)



Keys to Grade of Recommendations for Hypertension Diagnosis and Treatment

Grade

A	High levels of internal validity and statistical precision
B/C	Lower levels of internal validity and statistical precision
D	Expert opinion

Diagnosis

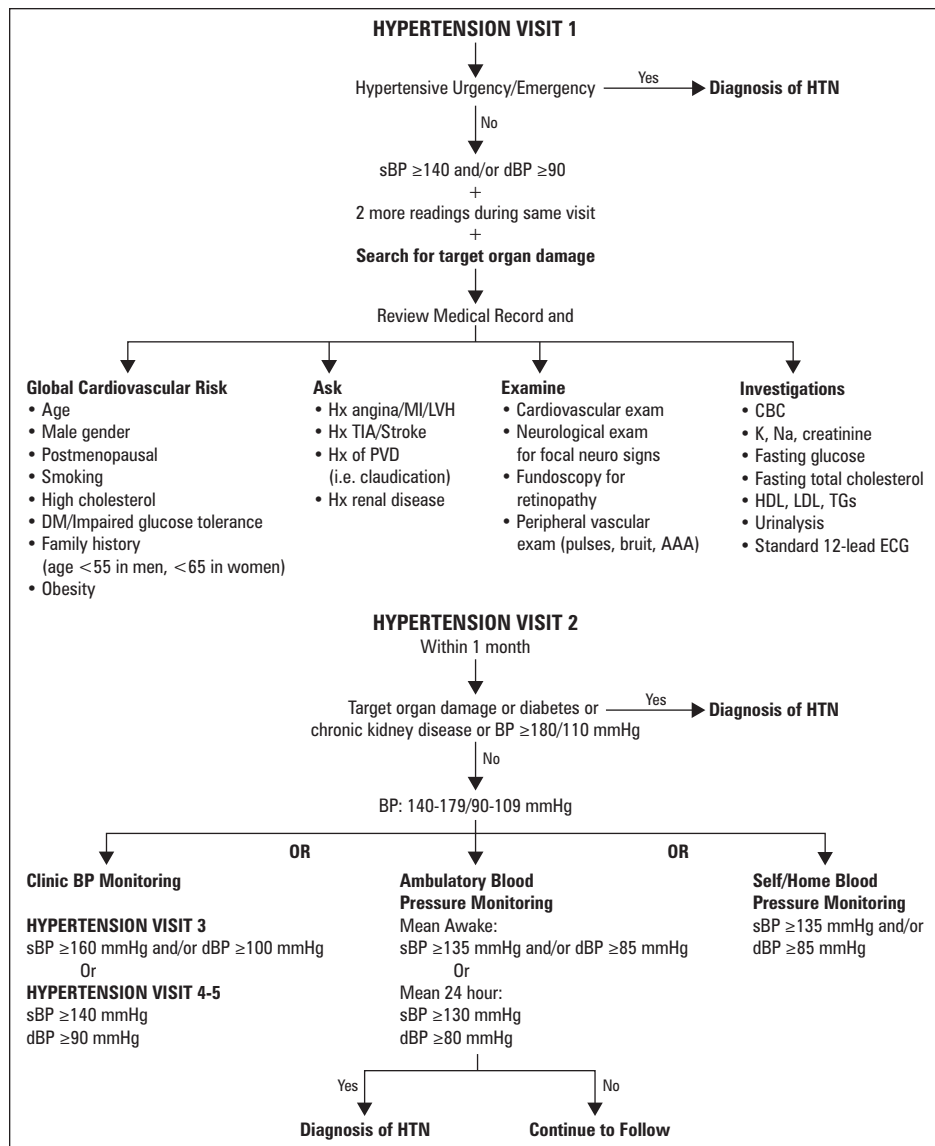


Figure 9. Approach to Hypertension

Adapted from: *The Canadian Journal of Cardiology* 2006;22(7):577.

Treatment

- target BP is <140/90 mmHg, <130/80 if DM or chronic kidney disease
- lifestyle modification (in all HTN patients)
 - may be sufficient in patients with stage 1 HTN (140-159/90-99)
 - diet
 - ♦ follow Canada's Guide to Healthy Eating (see *Nutrition*, FM4) and DASH (reduced cholesterol and saturated fats) (B)
 - ♦ limit daily sodium intake to 65-100 mmol (1.5-2.3 g) (B)
 - ♦ potassium/magnesium/calcium supplementations are NOT recommended for HTN (B)
 - moderate intensity dynamic exercise: 30-60 minutes, 4-7 x/week (D); higher intensity exercise is no more effective (D)
 - smoking cessation
 - low-risk alcohol consumption (see *Alcohol*, FM10) (B)
 - achieve and maintain a healthy BMI (18.5-24.9) and waist circumference (<102 cm for men, <88 cm for women) (C); BP will decrease by 4.0/2.8 mmHg for each 4.4 kg of weight loss; use multidisciplinary approach to weight loss (B)
 - individualized cognitive behavioural interventions for stress management (B)

The Effects of Lifestyle Modification on Diet, Weight, Physical Fitness and Blood Pressure Control. 18-month Follow-up Results from the PREMIER Collaborative Research Group

Ann Intern Med 2006; 144(7):127

Purpose: To compare effects of 2 lifestyle modification interventions compared to advice only on hypertension status, blood pressure, and lifestyle changes.

Study: Multicentre, randomized trial.

Patients: 810 adults with prehypertension or stage 1 hypertension (sBP 120-159, dBP 80-95)

Interventions: Multicomponent behavioural intervention using established recommendations ("established") arm, established recommendations plus the Dietary Approaches to Stop Hypertension (DASH) diet ("established + DASH") arm, and advice only arm.

Main outcomes: Lifestyle status and blood pressure.

Results: At 18 months, absolute blood pressures were reduced for both intervention arms compared to advice only but differences were non-significant. The odds for hypertension at 18 months were reduced for both treatment arms compared to advice only. Statistically significant weight loss, fat intake and sodium intake were noted for both treatment arms.

Dieting to Reduce Body Weight for Controlling Hypertension in Adults

Cochrane Database of Systemic Reviews 1998:

Issue 4

A systematic review of eighteen trials showed that weight-reducing diets in overweight hypertensive persons can affect modest weight loss in the range of 3-9% of body weight and are probably associated with modest blood pressure decreases of roughly 3 mmHg systolic and diastolic. Weight-reducing diets may decrease dosage requirements of persons taking antihypertensive medications.

Thiazides as First-Line Antihypertensive Therapy – ALLHAT

JAMA 2002; 288:2981-97

Study: Randomized, double-blind, active-controlled clinical trial with mean follow-up of 4.9 years.

Patients: 33,357 participants (mean age 67y, 53% male, 47% white) with stage 1 or 2 hypertension and at least one other CHD risk factor.

Intervention: Participants were randomly assigned to receive chlorthalidone (12.5-25mg/d), amlodipine (2.5-10mg/d), or lisinopril (10-40mg/d). Target BP was <140/90 mmHg, achieved by titrating the assigned study drug, and adding open-label agents when necessary.

Outcomes: The primary outcome was combined fatal CHD or non-fatal MI. Secondary outcomes were all-cause mortality, stroke, combined CHD, and combined CVD.

Results: There were no significant differences in either the primary outcome or all-cause mortality between treatment groups. For amlodipine vs. chlorthalidone, secondary outcomes were similar except for a higher 6-year rate of heart failure with amlodipine (10.2% vs. 7.7%; p<0.001). For lisinopril vs. chlorthalidone, lisinopril had higher 6-year rates of combined CVD (33.3% vs. 30.9%; p<0.001), stroke (6.3% vs. 5.6%; p=0.02) and heart failure (8.7% vs. 7.7%; p<0.001).

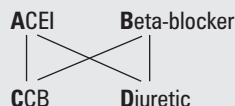
Conclusion: Thiazide-type diuretics are superior to CCB and ACEI for preventing one or more major forms of CVD, with similar risks of death and non-fatal MI.

**Calcium Channel Blockers****Dihydropyridine CCBs**

- amlodipine
- nifedipine
- felodipine

Non-dihydropyridine CCBs

- diltiazem
- verapamil

**How to Combine Antihypertensive Medications**

- pharmacological
 - indications regardless of age, be cautious with frail elderly patients
 - ♦ dBP ≥ 90 mmHg with target organ damage or independent cardiovascular risk factors (A)
 - ♦ dBP ≥ 100 mmHg (A) or sBP ≥ 160 mmHg (A) without target organ damage or cardiovascular risk factors
 - ♦ sBP ≥ 140 with target organ damage
- if partial response to standard dose monotherapy, add another first-line drug (C)
- caution with combination of non-DHP CCB and beta-blocker (D)
- combination of ACE inhibitor and ARB is not recommended (A)
- if still not controlled or adverse effects, can add other classes of anti-hypertensives (D)
- choice of therapy in patients with unique conditions (see Table 30)
- most patients will require combination therapy for optimal control

Follow-Up

- assess and encourage adherence to pharmacological and non-pharmacological therapy at every visit
- lifestyle modification \rightarrow q3-6 months
- pharmacological
 - q1-2 months until BP under target for 2 consecutive visits
 - more often for symptomatic HTN, severe HTN, antihypertensive drug intolerance, target organ damage
 - q3-6 months once at target BP
- referral is indicated for cases of refractory hypertension, suspected secondary cause or worsening renal failure
- hospitalization is indicated for malignant hypertension

Table 30. Pharmacologic Treatment of Hypertension in Patients with Unique Conditions

Condition or Risk Factor	Recommended Drugs	Alternative Drugs	Not Recommended
Isolated Diastolic HTN	Thiazide diuretic	β -blockers (age < 60) ACEI or ARB or CCB	α -blocker, β -blocker monotherapy (age > 60)
Isolated Systolic HTN	Monotherapy with low dose diuretics	Long acting dihydropyridine CCB or ARB	α -blocker, monotherapy with β -blockers
Ischemic Heart Disease (IHD)	ACEI	β -blockers or long-acting CCB if stable angina	Short-acting CCB (nifedipine) ACEI + ARB if no co-existing systolic heart failure
Recent STEMI or NSTEMI	β -blocker + ACEI	ARB (if intolerant to ACEI) Long-acting CCB if β -blocker is contraindicated or ineffective	Non-DHP CCB if evidence of heart failure
Left Ventricular Hypertrophy	Long-acting CCB, or thiazide diuretic		Direct arterial vasodilators: hydralazine, minoxidil
Cerebrovascular Disease (stroke/TIA)	ACEI + diuretic		ACEI + ARB after a stroke
Systolic Dysfunction	ACEI + β -blockers (diuretics as additive therapy) Aldosterone antagonists for NYHA Class III/IV or post-MI ACEI + ARB (uncontrolled HTN)	ARB (if intolerant to ACEI) Hydralazine + isosorbide dinitrate (if ACEI + ARB contraindicated) Long-acting CCB	Non-DHP CCB Carefully monitor for s/e if using ACEI + ARB
Dyslipidemias	As for uncomplicated IHD	As for uncomplicated IHD	β -blockers without ISA
Peripheral Vascular Disease	β -blockers (if severe disease)	As for uncomplicated IHD	As for uncomplicated IHD
Diabetes Mellitus with Nephropathy (urinary albumin ≥ 30 mg/d)	ACEI or ARB	Add other anti-hypertensives	α -blocker
Diabetes Mellitus without Nephropathy (ACR < 2.0 mg/mmol for men, < 2.8 for women)	ACEI, ARB, DHP CCB, or thiazide	Cardioselective β -blockers or non-DHP CCB Can add other first-line agents	If creatinine > 150 μ mol/L, use loop diuretic instead of thiazide diuretic ACEI + ARB if normal urine albumin
Non-diabetic Chronic Kidney Disease	ACEI (thiazide diuretics as additive therapy)	Can add thiazide diuretic Loop diuretics if volume overload	ACEI + ARB
Renovascular Disease	Same as HTN without other indications		Caution with ACEI or ARB due to risk of ARF
Asthma	K-sparing + thiazide diuretics for patients on salbutamol		β -blockers, unless specific indications like angina or post-MI
Gout			Thiazides, but asymptomatic hyperuricemia is not a contraindication

Table 30. Pharmacologic Treatment of Hypertension in Patients with Unique Conditions (continued)

Condition or Risk Factor	Recommended Drugs	Alternative Drugs	Not Recommended
Smoking	Low dose thiazides ACEI		β -blockers
Pregnancy	Methyldopa Hydralazine	Labetolol Nifedipine	ACEI
Elderly (>60)	As for uncomplicated IHD, except for use of β -blockers		β -blockers not recommended as first line treatment
Emergency	(BP > 169/90) = labetalol, nifedipine		
If > 3 cardiovascular RFs or established atherosclerotic disease	Statin, ASA		Caution with use of ASA in patients with uncontrolled BP

ISA = intrinsic sympathomimetic activity, ARB = angiotensin II receptor blockers, ACEI = angiotensin converting enzyme inhibitor

Adapted from: McAlister FA, Zarnke KB, Campbell NRC, et al. (2002). The 2001 Canadian recommendations for the management of hypertension: Part two – Therapy. *Can J Cardiol*, 18(6):625-641. AND The 2010 Canadian Hypertension Education Program Recommendations.

Low Back Pain

- see Orthopaedics, OR23

Definition

- acute: <6 weeks
- subacute: 6-12 weeks
- chronic: >12 weeks

Epidemiology

- 5th most common reason for visiting a physician
- lifetime prevalence: 90%
- peak prevalence: age 45-60
- largest WSIB category
- most common cause of chronic disability for persons <45 years old
- 90% resolve in 6 weeks, <5% become chronic

Etiology

- source of pain can be local, radicular, referred, or related to a psychiatric illness
- 98% mechanical cause
 - ligamentous/muscle strain, facet joint degeneration, disc injury, spondylosis, spondylolisthesis, compression fracture, spinal stenosis, pregnancy
 - worse with movement, improved with rest
- 2% non-mechanical cause
 - most concerning when pain is worse at rest and does not change with position
- surgical emergencies
 - cauda equina syndrome: low back pain, areflexia, lower extremity weakness, fecal incontinence, urinary retention, saddle anesthesia, decreased anal tone
 - abdominal aortic aneurysm: pulsatile abdominal mass
- medical conditions
 - neoplastic (primary, metastatic, multiple myeloma)
 - infectious (osteomyelitis, TB)
 - metabolic (osteoporosis, osteomalacia, Paget's disease)
 - rheumatologic (ankylosing spondylitis, polymyalgia rheumatica)
 - referred pain (perforated ulcer, pancreatitis, pyelonephritis, ectopic pregnancy, herpes zoster), no change with position

Physical Exam

- neurologic exam for L4, L5, S1 helps determine level of spinal involvement (muscle strength, sensation, reflexes)
- peripheral pulses
- special tests
 - straight leg raise (positive if pain at <70 degrees, aggravated by dorsiflexion of ankle), positive test is indicative of sciatica
 - crossed straight leg raise (more specific; raising of uninvolved leg elicits pain in leg with sciatica)
 - femoral stretch test (patient prone, knee flexed, examiner extends hip) to diagnose L4 radiculopathy



Red Flags for Back Pain

Bowel or bladder dysfunction
Anesthesia (saddle)
Constitutional symptoms/malignancy
Chronic disease
Paresthesias
Age >50 and mild trauma
IV drug use
Neuromotor deficits

Spinal Manipulative Therapy for Low Back Pain

Cochrane Database of Systematic Reviews 2004; Issue 1

Methods: Systematic review of 39 RCTs that compared spinal manipulative therapy with other therapies for low back pain.

Findings: For acute and chronic low back pain, spinal manipulative therapy was superior only to sham therapy or therapies judged to be ineffective or even harmful. It had no statistical or clinical advantage over analgesics, physical therapy, exercises, back school or physician care.

Conclusions: For acute and chronic low-back pain, there is no evidence that spinal manipulative therapy is superior to other treatments.

Massage for Low Back Pain

Cochrane Database of Systematic Reviews 2008; Issue 4

This meta-analysis of 13 randomized trials assessed the use of massage therapy for non-specific low back pain compared to other active or sham treatments.

Reviewer's Conclusions: For some patients with subacute or chronic non-specific low back pain, massage may be beneficial – especially with education and exercises. Some evidence suggests that acupuncture massage may be more effective than classic massage but more studies are required to confirm these results.

Non-steroidal Anti-inflammatory Drugs for Low Back Pain

Cochrane Database of Systematic Reviews 2008; Issue 1

This systematic review of 65 randomized and double-blind controlled trials assessed the effects of NSAIDs in treating non-specific low back pain and whether one type of NSAID was more effective.

Reviewer's Conclusions: In acute and chronic low back pain without sciatica, NSAIDs are slightly effective for short-term symptomatic relief. There was no difference between NSAIDs and placebo in patients with acute sciatica. No specific type of NSAID appears to be better.

Acupuncture and Dry-needling for Low Back Pain

Cochrane Database of Systematic Reviews 2005; Issue 1

This systematic review of 35 randomized control trials investigated the effectiveness of acupuncture on low back pain (LBP).

Conclusions: Effectiveness of acupuncture for acute LBP could not be assessed due to poor study design and low sample sizes. However, acupuncture is more effective for pain relief and functional improvement of chronic LBP than no treatment or sham treatment. Although acupuncture is not more effective than other therapies, it may be useful as an adjunct. Higher quality trials are needed.

Investigations

- plain films not recommended in initial evaluation
- indications for lumbar spine x-ray
 - no improvement after 1 month
 - fever >38°C
 - unexplained weight loss
 - prolonged corticosteroid use
 - significant trauma
 - progressive neuromotor deficit
 - suspicion of ankylosing spondylitis
 - history of cancer (rule out metastases)
 - alcohol/drug abuse (increased risk of osteomyelitis, trauma, fracture)
- CBC, ESR, urinalysis (infection, cancer)
- bone scan (infection, tumour, occult fracture), EMG if indicated
- consider CT or MRI (worsening neurologic deficits, infection, tumour)

Treatment

- reassurance and education if no underlying serious condition
 - 70% improve in 2 weeks, 90% in 6 weeks
- recommend comfort measures/conservative
 - limited bed rest (>2-4 days bed rest has potentially debilitating effects and no proven efficacy)
 - staying active (within limits of pain) leads to more rapid recovery and less chronic disability
 - activity modification (temporarily avoid activities that stress spine, e.g. heavy lifting, prolonged unsupported sitting)
 - heat or cold therapies
 - notes for work or WSIB to endorse “modified, appropriate work” vs. time off
 - encourage early return to work or activities
 - short course of massage may be beneficial
 - NO proven efficacy of spinal traction, TENS, biofeedback, injections (trigger-point, facet joint) or spinal manipulation; some evidence that acupuncture may be a helpful adjunct to other therapies
- pharmacological
 - acetaminophen
 - NSAIDs
 - muscle relaxants sometimes helpful but may cause drowsiness and are no better than NSAIDs; short term muscle relaxant use <7 days may be helpful
 - NOT narcotics
- if no improvement after one month of conservative therapy, consider further investigations
 - x-rays and appropriate labs in presence of any red flags
- surgical evaluation if
 - suspected cauda equina syndrome
 - worsening neurologic deficit
 - intractable pain not responding to conservative therapy

Table 31. Approach to Non-traumatic Low Back Pain

	Back dominant (Pain greatest above gluteal fold)		Leg dominant (Pain greatest below gluteal fold)	
History	Pattern 1 Worse with flexion Constant/intermittent	Pattern 2 Worse with extension Never worse with flexion Always intermittent	Pattern 3 Pain changes with back movement/position Currently/previously constant	Pattern 4 Worse with activity Improves with rest and posture change Intermittent/short duration
Physical Exam	Normal neuro exam <u>Fast responder</u> • Improves with extension <u>Slow responder</u> • No change or worsens with extension	Normal neuro exam ± improves with flexion	Leg pain can improve but not disappear Positive straight leg raise ± conduction loss <u>Fast responder</u> • Improves with specific back position <u>Slow responder</u> • Not better with position changes	No irritative findings ± conductive loss
Likely Pathology	Arising from intervertebral discs or adjacent ligaments	Posterior joint complex (associated ligaments and capsular structures)	Sciatica	Neurogenic claudication
Initial Management	Scheduled extension Lumbar roll Night lumbar roll Medication as required	Scheduled flexion Limited extension Night lumbar roll Medication as required	Prone extension Supine “Z” lie Lumbar roll Night lumbar roll Medication as required	Abdominal exercises Night lumbar roll Sustained flexion Medication as required

Adapted from: American Academy of Orthopaedic Surgeons. Acute Care: Nontraumatic Low Back Pain. *Orthopaedic Knowledge Update: Spine 2* 2001; 153-166

Menopause/HRT

- see Gynecology, GY32

Epidemiology

- mean age of menopause = 51.4 years
- a woman will spend over 1/3 of her life in menopause

Clinical Features

- urogenital tract: atrophy, vaginal dryness, incontinence
- blood vessels and heart: vasomotor instability, hot flashes, increased risk of heart disease
- bones: bone loss, fractures, loss of height
- brain: depression, mood swings, memory loss

Management

- encourage physical exercise, smoking cessation, and a balanced diet with adequate intake/supplementation of calcium/vitamin D (1500 mg/800 IU OD)
- hormone replacement therapy (HRT)
 - routine use of HRT is no longer recommended
 - regimens: cyclic estrogen + progesterone, continuous estrogen + progesterone, estrogen only (no uterus), estrogen ring, estrogen gel
 - helps with symptomatic relief of estrogen deprivation
 - decreases risk of osteoporotic fractures, colorectal cancer
 - increases risk of breast cancer, coronary heart disease, stroke, and pulmonary embolism
 - initiation of HRT requires a thorough discussion of each patient's history, symptoms and risk factors, and of the overall short and long-term benefits and risks
- consider venlafaxine, SSRI, gabapentin to ease vasomotor instability

Estrogen Plus Progestin and the Risk of Coronary Heart Disease

NEJM 2003; 349(6):523-34

Study: Randomized controlled trial, after a mean follow-up of 5.2 years. Planned duration was 8.5 years but the data and safety monitoring board recommended terminating the trial because the overall risks exceeded the benefits.

Patients: 16,608 postmenopausal women, age 50 to 79 years at base line.

Intervention: Conjugated equine estrogens (0.625 mg per day) plus medroxyprogesterone acetate (2.5 mg per day) or placebo.

Purpose: Final results with regard to estrogen plus progestin and CHD from the Women's Health Initiative (WHI).

Main Outcomes: Nonfatal MI or death due to coronary heart disease.

Results: Combined HRT was associated with a hazard ratio for coronary artery disease of 1.24. The elevation in risk was most apparent at one year (hazard ratio 1.81).

Conclusions: Estrogen plus progestin does not confer cardiac protection and may increase the risk of CHD among generally healthy postmenopausal women, especially during the first year after the initiation of hormone use. This treatment should not be prescribed for the prevention of cardiovascular disease.

Osteoarthritis

- see Rheumatology, RH4

Epidemiology

- most common form of arthritis seen in primary care
- prevalence: 10-12%, increases with age
- results in long-term disability in 2-3% of patients with OA
- almost everyone over the age of 65 shows signs of OA on x-ray, but only 33% of these will be symptomatic

Clinical Features

- pain with weight bearing, improved with rest
- morning stiffness or gelling <30 min
- deformity, bony enlargement, crepitus, limitation of movement
- usually affects distal joints of hands, spine, hips, and knees

Investigations

- no laboratory tests for the diagnosis of OA
- radiographic features: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes

Management

- goals: relieve pain, preserve joint motion and function, prevent further injury
- conservative
 - patient education, weight loss, exercise (OT/PT), assistive devices (canes, orthotics, raised toilet seats)
- pharmacological
 - keep in mind co-morbid conditions such as HTN, peptic ulcer disease, renal disease
 - medications do not alter natural course of OA
 - 1st line: acetaminophen 325-1000 mg qid prn (OA is not an inflammatory disorder)
 - 2nd line: NSAIDs [COX-2 selective NSAIDs (Celebrex®, Mobicox®) recommended if long-term therapy or if high risk for serious GI problems]
 - combination analgesics (e.g. acetaminophen and codeine)
 - intra-articular corticosteroid injections (not more than 3-4x/yr) may be helpful in acute flares (benefits last 4-6 wks, can be up to 6 mo)
 - intra-articular hyaluronic acid injections
 - topical NSAID (Pennsaid®)
 - capsaicin cream (Zostrix®)
- surgery
 - consider if persistent significant pain and functional impairment despite optimal pharmacotherapy (e.g. debridement, osteotomy, total joint arthroplasty)



- Hand (DIP, PIP, 1st CMC)
- Hip
- Knee
- 1st MTP
- L-spine (L4-L5, L5-S1)
- C-spine
- Uncommon: ankle, shoulder, elbow, MCP, rest of wrist

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Figure 10. Common Sites of Involvement in OA

Glucosamine Therapy for Treating Osteoarthritis

Cochrane Database of Systematic Reviews 2005; Issue 2

This meta-analysis of 25 single- and double-blinded randomized controlled trials with 4963 patients compared glucosamine treatment, administered by any route, against placebo or another treatment.

Reviewer's Conclusions: Glucosamine can decrease pain and functional impairment resulting from OA and is not associated with any side effects compared to placebo. Differences in the effectiveness of Rotta and non-Rotta preparations highlight variability between glucosamine preparations and patients should be made aware of this.

Osteoporosis

- see [Endocrinology](#), E43
- age-related disease characterized by decreased bone mass and increased susceptibility to fractures
- affects 1 in 4 Canadian women and 1 in 8 Canadian men

Table 32. Risk Factors for Osteoporosis

Major Risk Factors	Minor Risk Factors
Age >65 years	Rheumatoid arthritis
Vertebral compression fracture	Past history of clinical hyperthyroidism
Fragility fracture after age 40	Chronic anticonvulsant therapy
Family history of osteoporotic fracture (especially maternal hip fracture)	Low dietary calcium intake
Systemic glucocorticoid therapy of >3 months duration	Smoker
Malabsorption syndrome	Excessive alcohol intake
Primary hyperparathyroidism	Excessive caffeine intake
Propensity to fall	Weight <57 kg
Osteopenia apparent on x-ray film	Weight loss >10% of weight at age 25
Hypogonadism	Chronic heparin therapy
Early menopause (before age 45)	

Diagnosis

- defined in terms of a bone mineral density (BMD) T-score < -2.5 SD
- osteopenia: BMD T-score between -1.0 SD and -2.5 SD
- mass BMD screening is not recommended
- measure BMD in
 - all patients >65 years of age
 - all patients with one major or two minor risk factors for osteoporosis (see Table 32)
- measure BMD using dual x-ray absorptiometry (DEXA)
- suspect osteoporosis in women with back pain, a decrease in height or thoracic kyphosis

Management

- institute a fall prevention program for those at risk; optimize eyesight
- lifestyle
 - weight bearing exercise, smoking cessation, decrease alcohol intake
- diet
 - for women without documented osteoporosis, calcium and vitamin D supplementation alone prevents osteoporotic fractures (grade B recommendation)
 - calcium (1500 mg/day) and vitamin D (800 IU/day) intake in diet or supplements
- pharmacological
 - women with osteoporosis: bisphosphonates (e.g. risedronate, alendronate) or Selective Estrogen Receptor Modulators (e.g. raloxifene) prevent osteoporotic fractures (grade A to B recommendation)
 - women with severe osteoporosis (osteoporosis plus at least 1 fragility fracture): alendronate, risedronate, parathyroid hormone (limited duration), raloxifene, etidronate and oral pamidronate therapy (grade A to B recommendation)
 - if none of these drugs is tolerated, hormone replacement therapy (HRT) or calcitonin can be considered
 - severe esophagitis is the major side effect of bisphosphonate use
- HRT, calcitonin
 - there is fair evidence that combined estrogen-progestin therapy decreases the incidence of total, hip and nonvertebral fractures; however, for most women the risks may outweigh the benefits (grade D recommendation), see [Gynecology](#), GY33



Calcium Content of Some Common Food

1 cup milk – 300 mg
 ¾ cup yogurt – 295 mg
 ½ can salmon w/bones – 240 mg
 ¾ cup cooked broccoli – 50 mg
 1 medium orange – 50 mg

Osteoporosis Society of Canada.
www.osteoporosis.ca



DDx of Rash

- Contact dermatitis
- Herpes zoster
- Eczema
- Erythema nodosum
- Lichen planus
- Psoriasis
- Lupus erythematosus
- Drug reaction

Rash

- see [Dermatology](#), D4

History

- age
- duration of lesions
- associated symptoms: itching, fever, pain
- travel history
- sick contacts
- past medical history, medications, sexual history
- vaccinations

Physical Exam

- vitals
- describe lesion (SCALD)
 - Size
 - Colour (e.g. hyperpigmented, hypopigmented, erythematous)
 - Arrangement (e.g. solitary, linear, reticulated, grouped, herpetiform)
 - Lesion morphology
 - Distribution (e.g. dermatomal, intertriginous, symmetrical/asymmetrical, follicular)

Investigations

- depends on history; may include swab of lesion, biopsy

Management

- depends on symptoms and cause of rash
- refer to dermatologist as needed

**Common DDx of Pruritic Rash**

- Eczema
- Contact dermatitis
- Insect bites
- Scabies
- Urticaria
- PUPPP (during pregnancy)
- Drug reaction

Rhinorrhea

- see Otolaryngology, OT23

Differential Diagnosis

- common cold, sinusitis, influenza, strep pharyngitis, ear infections, vasomotor rhinitis
- allergies, contact with substances/tearing
- foreign body
- opioid withdrawal
- basilar skull fracture

Investigations

- CBC, throat swab, nasopharyngeal swab, x-ray if injury, allergy testing

Management

- saline nasal rinse
- consider medications: antihistamines, decongestants, corticosteroid nasal spray

Sexually Transmitted Infections (STIs)



- see Gynecology, GY26

Definition

- diverse group of infections caused by multiple microbial pathogens
- transmitted by either secretions or fluids from mucosal surfaces

Epidemiology

- high incidence rates worldwide
- Canadian prevalence rates in clinical practice
 - common: chlamydia, gonorrhea, PID, genital warts, genital herpes (increasing incidence)
 - less common: hepatitis B, HIV & syphilis (both increasing in incidence), trichomoniasis
 - rare: chancroid, lymphogranuloma venereum, granuloma inguinale
- genital tract infections (NOT sexually transmitted): vulvovaginal candidiasis (VVC), bacterial vaginosis (BV)
- three most common infections associated with vaginal discharge in adult women are BV, VVC, and trichomoniasis

History

- sexual history
 - level of sexual activity and type (oral, anal and/or vaginal intercourse)
 - age of first intercourse, sexual orientation, sexual activity during travel
 - total number of partners in the past year/month/week and duration of involvement with each

**Risk Factors**

- Sexually active males and females <25 years old
- Early age of 1st intercourse
- Street involved and/or substance use, men who have sex with men
- Unprotected sex, previous STI, contact with known case of STI
- New partner in past 2 months, >2 partners in past 12 months



When a STI is detected in a prepubertal child, evaluation for sexual abuse is prudent.

Prophylactic Vaccination Against Human Papillomavirus Infection and Disease in Women: A Systematic Review of Randomized Controlled Trials

CMAJ 2007; 177(5):469-479.

Purpose: To evaluate prophylactic HPV vaccination in preventing high- and low-grade cervical lesions, persistent HPV infection, external genital lesions, adverse events, and death using meta-analysis.

Studies: 9 reports from 6 different trials with 40 323 patients were included and all studies were of high methodologic quality. Three studies used the quadrivalent vaccine, two used the bivalent, and one used a monovalent. The longest mean duration of follow-up was 48 months.

Results: Prophylactic HPV vaccination decreased the frequency of high-grade cervical lesions caused by vaccine-type HPV strains compared to the control group (Peto odds ratio 0.14 (95% CI 0.09-0.21)). Vaccinations also prevented persistent HPV infection, low-grade lesions and genital warts and the reported adverse events were mostly minor.

Compared to placebo, there was no difference in serious adverse events or death.

Conclusion: Prophylactic HPV is highly efficacious in preventing infection and precancerous cervical disease in women aged 15-25 who have not previously been infected with vaccine-type HPV strains.

- STI history
 - STI awareness, previous STIs and testing, partners with previous STIs
 - contraception history, last Pap test and results
 - local symptoms such as genital burning, itching, discharge, sores, vesicles
 - associated symptoms such as fever, arthralgia, lymphadenopathy
 - partner communication with regards to STIs

Investigations/Screening

- individuals at increased risk, even those who are asymptomatic, should be screened for chlamydia, gonorrhea, HIV, hepatitis B, and syphilis
- Pap test if none performed in the preceding 12 months

Management

- primary prevention is vastly more effective than treating STIs and their sequelae
- offer hepatitis B vaccine if not immune, offer Gardasil® to women under age of 26
- discuss STI risk factors (e.g. decreasing the number of sexual partners)
- direct advice to ALWAYS use condoms or to abstain from intercourse
- condoms not 100% effective against HPV, herpes, genital warts
- a STI patient is not considered treated until the management of his/her partner(s) is ensured (contact tracing by Public Health)
- patients should abstain from sexual activity until treatment completion
- mandatory reporting: chlamydia, gonorrhea, hepatitis B, HIV, syphilis

Table 33. Diagnosis and Treatment of Common STI

	Signs and Symptoms	Investigations	Treatment	Complications
Gonococcal Urethritis/Cervicitis (<i>Neisseria gonorrhoeae</i>)	M: burning, irritation, unexplained pyuria, urethral discharge F: mucopurulent endocervical discharge, dysuria, pelvic pain, vaginal bleeding M and F: often asymptomatic, can involve rectal symptoms in cases of unprotected anal sex	M: urine PCR, urethral swabs for stain and culture F: endocervical swab for culture, vaginal swab for wet mount and Gram stain	Cefixime 400 mg PO, single dose + non-gonococcal urethritis/cervicitis Rx* F/U in 2 wks for test of cure if symptoms persist	Arthritis, increased risk of acquiring and transmitting HIV M: urethral strictures, epididymitis, infertility F: PID, infertility, ectopic pregnancy, perinatal infection, chronic pelvic pain
Non-Gonococcal Urethritis/Cervicitis (Usually <i>Chlamydia trachomatis</i> **)	~70% asymptomatic If symptoms appear (usually 2-6 wks after infection) then similar to gonococcal symptoms (see above)	Same as above	Azithromycin 1 g PO, single dose + gonococcal urethritis/cervicitis Rx* Same follow up as above	Same as above
Human Papilloma Virus (genital warts)	Most are asymptomatic M: cauliflower lesions (condylomata acuminata) on skin/mucosa of penile/anal area F: cauliflower lesions AND/OR pre-neoplastic/neoplastic lesions on cervix, vagina, or vulva	None needed if simple condylomata Potential biopsy of suspicious lesions F: screening for cervical dysplasia through regular Pap smears	For condylomata: cryotherapy, electrocautery, topical therapy (podophyllotoxin) For cervical dysplasia: colposcopy and possible excision, dependent on grade of lesion	M + F: anal cancer F: cervical/vaginal/vulvar cancer M who have sex w/ M + F who have receptive anal sex: rectal CA
Genital Herpes (HSV-1 and -2)	1° episode: painful vesiculoculcerative genital lesions, ± tender lymphadenopathy and fever, protracted course Recurrent episodes: less extensive lesions, shorter course, may have "trigger factors"	Swab of vesicular content for culture, type-specific serologic testing for HSV-1 and HSV-2 antibodies	<u>1° episode:</u> Acyclovir 200 mg PO 5x/day for 5-10d, OR Famciclovir 250 mg PO tid for 5d, OR Valacyclovir 1000 mg PO bid for 10d <u>Recurrent Episodes:</u> Valacyclovir 500 mg PO bid OR 1 g qd for 3d, OR Famciclovir 125 mg PO bid for 5d, OR Acyclovir 200 mg PO 5x/d for 5d, or 800 mg PO tid for 2d	Genital pain, urethritis, aseptic meningitis, cervicitis, increased risk of acquiring and transmitting HIV
Infectious Syphilis (<i>Treponema pallidum</i>)	1°: painless sore 2°: rash and flu-like symptoms Latent Phase: asymptomatic 3°: neurologic, cardiovascular, and tissue complications	Specimen collection from 1° and 2° lesions; screen high risk individuals with serologic syphilis testing; universal screening of pregnant women	Benzathine penicillin G IM (dose depends on stage) Notify partners (last 3-12 mths) Continuous follow-up and testing until patients are seronegative	Increased risk of acquiring and transmitting HIV Chronic neurologic and cardiovascular sequelae

M = Males; F = Females

*N.B. if urethritis/cervicitis is suspected, always treat for both gonococcal and non-gonococcal types (i.e. Cefixime AND Azithromycin)

**Most common reportable STI in Canada

Sinusitis



- see Otolaryngology, OT25

Definition

- inflammation of the mucous membranes of the nasal cavity and paranasal sinuses, fluid within these cavities, and/or the underlying bone

Etiology

- classifications:
 - acute: <4 weeks
 - recurrent: 4 or more episodes per year, each lasting at least 10 days, with an absence of symptoms in between
 - chronic: ≥12 weeks
- common pathogens: rhinovirus, influenza, parainfluenza, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*

Risk Factors

- medical conditions: respiratory infections, allergic rhinitis, cystic fibrosis, immunodeficiency
- anatomic: deviated septum, polyps, adenoid hypertrophy, tumour
- irritants: environmental, tobacco smoke, air pollution, chlorine
- iatrogenic: topical decongestant overuse, cocaine, trauma

Investigations

- radiography is warranted only when the diagnosis of sinusitis is in doubt
- all patients with pronounced frontal headaches should have a radiograph performed to rule out frontal sinusitis
- CT scans are not cost-effective and should not be used routinely to diagnose sinusitis

Management

- acute sinusitis
 - 70% of patients will resolve without antibiotics
 - oral analgesics/antipyretics for pain/fever
 - nasal saline rinse and humidification may be beneficial
 - short-term use of topical or systemic decongestants may be useful adjuncts
 - antihistamines are contraindicated
 - antibiotics limited to those diagnosed with acute bacterial sinusitis through history and physical
 - ♦ 1st line: amoxicillin x 10 days (TMP-SMX or doxycycline if penicillin allergic)
 - ♦ 2nd line: amoxicillin+clavulanate, clarithromycin, azithromycin, cefuroxime
 - referral to ENT if
 - ♦ failure of second-line therapy
 - ♦ ≥3 episodes per year
 - ♦ development of complications (mucocoele, orbital extension, meningitis, intracranial abscess, venous sinus thrombosis)



Sinusitis Score

- Maxillary toothache (1)
 - History of coloured nasal discharge (1)
 - No improvement with decongestants (1)
 - Abnormal transillumination (1)
 - Purulent secretion on exam (1)
- Other signs: nasal congestion, facial pain/pressure

Probability of Sinusitis By Score

- 0 – 9%
- 1 – 21%
- 2 – 40%
- 3 – 63%
- 4 – 81%
- 5 – 92%

Ebell, MH. *Evidence-based diagnosis: a handbook of clinical prediction rules*. 2001.

Sleep Disorders



- see also Respirology, R32

Definition

- most often characterized by one of three complaints:
 - insomnia
 - ♦ difficulty falling asleep, difficulty maintaining sleep, early-morning wakening, non-refreshing sleep
 - parasomnias
 - ♦ night terrors, nightmares, restless leg syndrome, somnambulism (performing complex behaviour during sleep with eyes open but without memory of event)
 - excessive daytime sleepiness

Epidemiology

- 1/3 of patients in primary care setting have occasional sleep problems
- 10% have chronic sleep problems
- more common in women and with increasing age

Etiology

- primary sleep disorders
 - primary insomnia, obstructive sleep apnea, restless legs syndrome, narcolepsy, periodic limb movements of sleep

- secondary causes
 - medical: COPD, asthma, CHF, hyperthyroidism, chronic pain, BPH
 - drugs: alcohol, caffeine, nicotine, beta-agonists, antidepressants, steroids
 - psychiatric disorders: especially mood and anxiety disorders
 - lifestyle factors: shift work

Investigations

- complete sleep diary every morning for 1-2 wks
 - record bedtime, sleep latency, total sleep time, awakenings, quality of sleep
- rule out specific medical problems (CBC + differential, TSH)
- sleep study referral if suspect periodic leg movements of sleep or sleep apnea
- night time polysomnogram or daytime multiple sleep latency test

Treatment

- treat any suspected medical or psychiatric cause
- psychologic treatment
 - sleep hygiene: avoid caffeine, nicotine, alcohol; exercise regularly; comfortable sleep environment; regular sleep schedule; no napping
 - relaxation therapy: deep breathing, meditation, biofeedback
 - stimulus control therapy: re-association of bed/bedroom with sleep; re-establishment of a consistent sleep-wake schedule; reduce activities that cue staying awake
 - sleep restriction therapy: total time in bed should closely match the total sleep time of the patient (improves sleep efficacy)
- pharmacologic treatment
 - short-acting benzodiazepines: e.g. lorazepam, oxazepam, temazepam, should be used <7 consecutive nights to break cycle of chronic insomnia

Specific Problems

- primary insomnia
 - majority of cases
 - person reacts to insomnia with fear or anxiety around bedtime or with a change in sleep hygiene; can progress to a chronic disorder (psychophysiological insomnia)
- snoring
 - results from soft tissue vibration at the back of the nose and throat due to turbulent airflow through narrowed air passages
 - risk factors: male gender, obesity, alcohol consumption, ingestion of tranquilizers or muscle relaxants, and smoking
 - PE: obesity, nasal polyps, septal deviation, hypertrophy of the nasal turbinates, and enlarged uvula and tonsils
 - investigations (only if severely symptomatic): nocturnal polysomnography and airway assessment (CT/MRI)
 - treatment
 - ♦ sleep on side (position therapy), weight loss
 - ♦ nasal dilators (noninvasive external dilator made with elastic adhesive backing applied over nasal bridge), tongue-retaining devices, mandibular advancement devices
 - at risk of developing obstructive sleep apnea
- obstructive sleep apnea (OSA)
 - apnea resulting from upper airway obstruction due to collapse of the base of the tongue, soft palate with uvula, and epiglottis
 - respiratory effort is present
 - leads to a distinctive snorting, choking, awakening type pattern as body rouses itself to open airway = resuscitative breath
 - apneic episodes can last from 20 sec to 3 min; can have 100-600 episodes/night
 - diagnosis based on nocturnal polysomnography: >15 apneic episodes per hour of sleep with arousal recorded
 - consequences
 - ♦ daytime somnolence, non-restorative sleep
 - ♦ poor social and work performance
 - ♦ mood changes: anxiety, irritability, depression
 - ♦ sexual dysfunction: poor libido, impotence
 - ♦ morning headache (due to hypercapnia)
 - ♦ HTN (2x increased risk), CAD (3x increased risk), stroke (4x increased risk), arrhythmias
 - ♦ pulmonary hypertension, RV dysfunction, cor pulmonale (due to chronic hypoxemia)
 - ♦ memory loss, decreased concentration, confusion
 - investigations
 - ♦ blood gas not helpful, TSH if clinically indicated
 - ♦ evaluate BP, inspect nose, oropharynx (i.e. for enlarged adenoids or tonsils)
 - ♦ nocturnal polysomnography (sleep lab)



Risk Factors for Obstructive Sleep Apnea

- 2% women, 4% men between ages 30-60
- Obesity causing upper airway narrowing: BMI >28 kg/m² present in 60-90% of cases
- Children: commonly tonsils, adenoids
- Aging which causes decreased muscle tone
- Persistent URTIs, allergies, nasal tumours, hypothyroidism (due to macroglossia)
- Family history

- treatment
 - ♦ modifying factors: avoid sleeping supine, lose weight, avoid alcohol, sedatives, narcotics, inhaled steroids if nasal swelling present
 - ♦ primary treatment of OSA is CPAP: maintains patent airway in 95% of OSA cases
 - ♦ dental appliances to modify mandibular position
 - ♦ surgery: somnoplasty, tonsillectomy and adenoidectomy (in children), uvulopalatopharyngoplasty (UPPP)
 - ♦ report patient to Ministry of Transportation if OSA is not controlled by CPAP
- central sleep apnea
 - definition
 - ♦ brain fails to send appropriate signals to the breathing muscles to initiate respirations
 - ♦ defining feature is absent respiratory effort
 - ♦ often secondary to CNS diseases: brainstem infarction, infection, neuromuscular disease
 - investigations: PFTs, nocturnal polysomnography, MRI
 - treatment: CPAP or mechanical ventilation (if brainstem origin)
 - prognosis: poor

Sore Throat (Pharyngitis)

Definition

- inflammation of the oropharynx
- may be caused by a wide range of infectious organisms, most of which produce a self-limited infection with no significant sequelae

Etiology

- viral
 - adenovirus, rhinovirus, influenza virus, RSV, EBV, coxsackie virus, herpes simplex virus, CMV, HIV
- bacterial
 - group A beta-hemolytic *Streptococcus* (GABHS)
 - group C and G beta-hemolytic *Streptococcus*, *Neisseria gonorrhoeae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Corynebacterium diphtheriae*

Epidemiology

- viral
 - most common cause, occurs year round
- bacterial
 - Group A beta-hemolytic *Streptococcus*
 - ♦ most common bacterial cause
 - ♦ 5-15% of adult cases and up to 50% of all pediatric cases of acute pharyngitis
 - ♦ most prevalent between 5-17 years old
 - ♦ occurs most often in winter months

Clinical Features

- viral
 - pharyngitis, conjunctivitis, rhinorrhea, hoarseness, cough
 - nonspecific flu-like symptoms such as fever, malaise, and myalgia
 - often mimics bacterial infection
 - coxsackie virus (hand, foot and mouth disease)
 - ♦ primarily late summer, early fall
 - ♦ sudden onset of fever, pharyngitis, headache, abdominal pain and vomiting
 - ♦ appearance of small vesicles that rupture and ulcerate on soft palate, tonsils, pharynx
 - ♦ ulcers are pale gray, several mm in diameter, have surrounding erythema, may appear on hands and feet
 - herpes simplex virus
 - ♦ like coxsackie virus but ulcers are fewer and larger
 - EBV (infectious mononucleosis)
 - ♦ pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash
- bacterial
 - symptoms: sore throat, absence of cough, fever, malaise, headache, abdominal pain
 - signs: fever, tonsillar or pharyngeal erythema/exudate, swollen/tender anterior cervical nodes
 - complications
 - ♦ rheumatic fever
 - ♦ glomerulonephritis
 - ♦ suppurative complications (abscess, sinusitis, otitis media, pneumonia, cervical adenitis)
 - ♦ meningitis
 - ♦ impetigo



Red Flags in Patients with "Sore Throat"

1. Persistence of symptoms longer than 1 week without improvement
2. Respiratory difficulty, particularly stridor
3. Difficulty in handling secretions (peritonsillar abscess)
4. Difficulty in swallowing (Ludwig's angina)
5. Severe pain in the absence of erythema (supraglottitis/epiglottitis)
6. A palpable mass (neoplasm)
7. Blood in the pharynx or ear (trauma)

Investigations

- suspected GABHS
 - see Table 34 for approach to diagnosis and management of GABHS
 - gold standard for diagnosis is throat culture
 - rapid test for streptococcal antigen: high specificity (95%), low sensitivity (50-90%)
 - ♦ if rapid test positive, treat patient
 - ♦ if rapid test negative, take culture and call patient if culture positive to start antibiotics
 - suspected EBV (infectious mononucleosis)
 - ♦ peripheral blood smear, heterophile antibody test (i.e. the latex agglutination assay, or “monospot”)

Table 34. Sore Throat Score: Approach to Diagnosis and Management of GABHS

	POINTS				
Cough absent?					1
History of fever >38°C?					1
Tonsillar exudate?					1
Swollen, tender anterior nodes?					1
Age 3-14 years?					1
Age 15-44 years?					0
Age >45 years?					-1
In communities with moderate levels of strep infection (10-20% of sore throats):					
Score	0	1	2	3	4
Chance patient has strep	2-3%	3-7%	8-16%	19-34%	41-61%
Suggested action	NO culture or antibiotic		Culture all, treat only if culture is positive		Culture all, treat with antibiotics on clinical grounds ¹

¹Clinical grounds include a high fever or other indicators that the patient is clinically unwell and is presenting early in the course of the illness.

Limitations: *This score is not applicable to patients less than 3 years of age.

*If an outbreak or epidemic of illness caused by GAS is occurring in any community, the score is invalid and should not be used.

Adapted from: Centor RM et al. *Med Decis Making* 1981; 1:239-46. McIsaac WJ, White D, Tannenbaum D, Low DE. *CMAJ* 1998; 158(1):75-83.

Management

- GABHS (see Table 34)
 - no increased incidence of rheumatic fever with 48-hour delay in treatment
 - incidence of glomerulonephritis is not decreased with antibiotic treatment
 - antibiotic treatment: see *Antimicrobial Quick Reference*, FM50
 - routine follow-up and/or post-treatment throat cultures are not required for most patients
 - follow-up throat culture recommended only for: patients with history of rheumatic fever, patients whose family member has history of acute rheumatic fever, suspected strep carrier
- viral pharyngitis
 - antibiotics NOT indicated
 - symptomatic therapy: acetaminophen/NSAIDs for fever and muscle aches, decongestants
- infectious mononucleosis (EBV)
 - antibiotics NOT indicated; administering ampicillin produces rash
 - self-limiting course; rest during acute phase is beneficial
 - if acute airway obstruction, give corticosteroids, consult ENT
 - supportive care, i.e. acetaminophen or NSAIDs for fever, sore throat, malaise
 - avoid heavy physical activity and contact sports for at least one month or until splenomegaly resolves because of risk of splenic rupture

Complementary and Alternative Medicine (CAM)

Epidemiology

- 50-75% of Canadians report some use of CAM over their lifetime, and only half will disclose this use to their physician
- use is highest in Western provinces, lowest in Atlantic provinces
- more likely to be used by younger patients, those with higher education and income
- examples: chiropractic, acupuncture, massage, naturopathy, homeopathy, traditional Chinese medicine, craniosacral therapy, osteopathy
- most commonly used for: back/neck problems, gynecological problems, anxiety, headaches, digestive problems and chronic fatigue syndromes

Herbal Products

- over 50% of Canadians use natural health products
- most commonly used include echinacea, ginseng, ginkgo, garlic, St John's Wort, and soy
- relatively few herbal products have been shown to be effective in clinical trials
- many patients believe herbal products are inherently safe and are unaware of potential side effects and interactions with conventional medicines
- all natural health products (NHPs) must be regulated under *The Natural Health Products Regulations* as of January 1, 2004, including herbal remedies, homeopathic medicines, vitamins, minerals, traditional medicines, probiotics, amino acids and essential fatty acids (e.g. omega-3)
- always ask patients whether they are taking any herbal product, herbal supplement or other natural remedy. Further questions may include:
 - Are you taking any prescription or non-prescription medications for the same purpose as the herbal product?
 - Are you allergic to any plant products?
 - Are you pregnant or breastfeeding?
- information resources: National Centre for CAM (www.nccam.nih.gov), Health Canada website

Table 35. Common Herbal Products

Common Name	Reported Uses	Possible Adverse Effects	Possible Drug Interactions
Black cohosh	Menopausal symptoms, PMS, labour induction, arthritis	Hepatitis, liver failure, headaches, GI discomfort, heaviness in legs, weight problems	None reported
Chamomile	Mild sedative, anxiolytic, GI complaints, common cold	Allergic/contact dermatitis, anaphylaxis	Anxiolytics, sedatives
Echinacea	Common cold, flu, wound treatment, urinary tract infections, cancer	Hypersensitivity, hepatotoxicity with prolonged use, avoid use if immunosuppressed	Potentiates warfarin
Evening primrose	Dysmenorrhea, menopausal sx, inflammation, allergies, eczema, arthritis, MS	Headache, restlessness, nausea, diarrhea, may decrease seizure threshold	Anticoagulants, antiplatelets
Feverfew	Migraine prevention, rheumatoid arthritis, anti-inflammatory	Anxiety, upset stomach, skin rash, miscarriage	Anticoagulants, antiplatelets
Flaxseed oil	Laxative, menopausal sx, source of omega-3 fatty acids	Diarrhea	Do not take with other medications as fibre content can bind drugs
Garlic	Elevated lipids, hypertension, hyperglycemia, antimicrobial	GI irritation, contact dermatitis, may increase post-op bleeding	Anticoagulants, potentiates antihypertensives
Ginger	Nausea, motion sickness, dyspepsia, anti-inflammatory	Heartburn, not to be used for morning sickness	None known
Ginkgo biloba	Increases peripheral circulation (AD, dementia, intermittent claudication), premenstrual syndrome, vertigo	Headache, cramping, bleeding, mild digestive problems; reports of intracranial hemorrhage	Anticoagulants, thiazide diuretics, MAO inhibitors
Ginseng	Energy enhancer, decreases stress, adjunct support for chemotherapy/radiation	Hypertension, nervousness, insomnia, breakthrough bleeding, palpitations	Stimulant medications, antihypertensives, hormonal therapies
Glucosamine (Chondroitin)	Osteoarthritis	GI distress, headache, drowsiness, palpitations	Caution if shellfish allergy
Saw palmetto	BPH, adjunct to finasteride	Mild GI distress	Alpha-adrenergics, finasteride
St. John's Wort	Mild to moderate depression	Photosensitivity, increased liver enzymes, drowsiness, dizziness, nausea, headaches	CNS depressants, C/I with indinavir
Valerian root	Sedative, anxiolytic, muscle relaxant, PMS	Drowsiness, headache, digestive problems, paradoxical insomnia	CNS depressants, antihistamines

References: Zink T, Chaffin J. Herbal "health" products: What family physicians need to know, *American Family Physician* 1998; 58(5):1133-1140.; NIH National Center for Complementary and Alternative Medicine website (<http://nccam.nih.gov>)

St. John's Wort for Depression

Cochrane Database of Systematic Reviews 2005; Issue 2

A meta-analysis of 37 trials, including 26 which compared St. John's Wort with placebo and 14 which compared St. John's Wort with standard antidepressants. The main outcome measure was the ratio of responders to non-responders, and the main outcome measure for adverse effects was the number of patients dropping out due to adverse experiences. Significant heterogeneity was noted among placebo-controlled trials, but trials were statistically homogeneous for trials comparing St. John's Wort with antidepressants. For major depression, compared with placebo, the OR for 6 larger trials was 1.15 (95% CI 1.02-1.29) and 5 smaller trials, 2.06 (95% CI 1.65-2.59). Compared with SSRIs and tricyclics, the response rates were 0.98 (95% CI 0.85-1.12) and 1.03 (95% CI 0.93-1.14), respectively. Fewer patients on St. John's Wort dropped out due to adverse effects compared to those taking tricyclics (OR 0.25; 95% CI 0.14-0.45), and a similar but non-significant trend was seen when compared with SSRIs (OR 0.60; 95% CI 0.31-1.15). Drawing solid conclusions is difficult given the degree of study heterogeneity and number of conflicting studies.

Primary Care Models

Table 36. Primary Care Models

	Characteristics
Comprehensive Care Model	<ul style="list-style-type: none"> Model for GPs in solo practice with limited after-hours availability
Family Health Team	<ul style="list-style-type: none"> Groups of health care professionals (e.g. GPs, RNs, NPs, dieticians, social workers) Wider range of services (e.g. rehabilitation, palliative care), with increased after-hours availability Receives provincial funding for allied health
Family Health Group	<ul style="list-style-type: none"> Group of ≥ 3 GPs, with some after-hours availability as well as on-call to telephone health advisory services Payment model: fee-for-service plus premiums
Family Health Network	<ul style="list-style-type: none"> Group of ≥ 3 GPs; can utilize nurse practitioners, with telephone health advisory services to provide around the clock primary care coverage Payment model: salary-based
Family Health Organization	<ul style="list-style-type: none"> Groups of GPs working with allied health, with after-hours clinics and 24h telephone health advisory services Payment model: fee-for-service plus premiums

Antimicrobial Quick Reference*

Condition	Microorganisms	Antimicrobial
RESPIRATORY/ENT		
Acute Rhinitis (common cold)	Viral: Rhinovirus, Adenovirus, RSV, Influenza, etc.	None
Pharyngitis (sore throat)	Viral: Adenovirus, Rhinovirus	None
Strep Pharyngitis	Group A beta-Hemolytic <i>Strep</i>	<p><i>Pediatric:</i></p> <p>pen V 25-50 mg/kg/d PO div. q6h x 10d amox/clav 45 mg/kg/d PO div. q12h x 10d clarithromycin 15 mg/kg/d PO div. bid x 10d azithromycin 12 mg/kg/d PO x 5d</p> <p><i>Adults:</i></p> <p>pen V 500mg PO bid or 250 mg qid x 10d cefuroxime 250 mg PO bid x 4d clarithromycin 250 mg PO bid x 10d azithromycin 500 mg PO once, then 250 mg daily x4d</p> <p>Penicillin allergy: erythromycin</p>
Sinusitis	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>M. catarrhalis</i> Group A <i>Strep</i> Anaerobes <i>S. aureus</i>	<p>1st line: amoxicillin 1 g PO tid x 10d (If penicillin allergy: TMP/SMX DS 1 tab PO bid)</p> <p>2nd line: amox/clavulin 2000/125 mg PO bid x 10d</p> <p>3rd line: clarithromycin XL 1000 mg PO OD x 10d</p>
Acute Otitis Media	Viral <i>S. pneumoniae</i> <i>H. influenzae</i> <i>M. catarrhalis</i>	<p>Treat if under 24 months old for 7d. If >24 months old, treat if worsens after 48-72h</p> <p><10 y.o.:</p> <p>1st line: amoxicillin 75-90 mg/kg/d PO tid x 5d 2nd line: amoxicillin/clavulin 3rd line: macrolides</p> <p>>10 y.o.: amoxicillin 500 mg PO tid x 7-10d penicillin allergy: cefuroxime, azithromycin, clarithromycin</p>
Otitis Externa	<i>Pseudomonas</i> <i>S. aureus</i> Fungal	<p>Diabetic:</p> <p>ciprofloxacin 500 mg PO bid x 14d</p> <p>Non-diabetic:</p> <p>1st line: Buro-sol® 2-3 drops tid 2nd line: Cortisporin® otic solution 4 drops tid</p>
Bronchitis	Viral: Rhinovirus, Coronavirus, Adenovirus, RSV, Influenza, Parainfluenza <i>S. pneumoniae</i> <i>H. influenzae</i> <i>M. pneumoniae</i> <i>C. pneumoniae</i>	Abx not recommended for acute bronchitis

Condition	Microorganisms	Antimicrobial
RESPIRATORY/ENT		
Community Acquired Pneumonia	Susceptible to beta-lactams: <i>S. pneumoniae</i> <i>H. influenzae</i> <i>S. aureus</i>	Adult dosing (no respiratory comorbidities): erythromycin 500 mg PO qid x 7-10d clarithromycin 250-500 mg PO bid x 7-10d azithromycin 500 mg PO 1st dose then 250 mg PO OD x 4d
	Not susceptible to beta-lactams: <i>Mycoplasma</i> <i>Chlamydia pneumoniae</i> <i>Legionella pneumoniae</i>	doxycycline 200 mg PO 1st dose then 100 mg PO bid x 7-10d
Dental Infections/ Periapical and Periodontal Abscesses	Oral Flora	Pen V potassium 500 mg PO qid x 7-10d clindamycin 300 mg PO qid x 7-10d
GASTROENTEROLOGY		
Diarrhea – Enteritis	<i>Shigella</i> <i>Salmonella</i> <i>Campylobacter</i> <i>E. coli</i> <i>Yersinia</i>	Abx if severe, treat according to specific organism isolated
Diarrhea – post abx (common with clindamycin)	<i>C. difficile</i>	Add metronidazole 500 mg PO tid x 10-14d or vancomycin 125 mg PO qid
Peptic Ulcer Disease (non-NSAID related)	<i>H. pylori</i>	HP-PAC (7 blister card pack): lansoprazole 30 mg PO bid + clarithromycin 500 mg PO bid + amoxicillin 1 g PO bid x 7d Penicillin allergy: metronidazole 500 mg PO bid + clarithromycin 250 mg PO bid + omeprazole 20 mg PO bid x 7-14d
GENITOURINARY		
UTI/Cystitis	<i>Klebsiella</i> <i>E. coli</i> <i>Enterobacter</i> <i>Enterococci</i> <i>Proteus</i> <i>S. saprophyticus</i>	<20% <i>E. coli</i> resistance to TMP-SMX: TMP-SMX 1 DS tablet PO bid x 3d >20% <i>E. coli</i> resistance to TMP-SMX: ciprofloxacin 250 mg PO bid or cipro ER 500mg daily x3d Nitrofurantoin (Macrobid®) 100 mg PO bid x 5d if sulfa allergy Pregnancy: amoxicillin 250-500 mg PO tid x 7d N.B. nitrofurantoin is contraindicated in pregnancy after 38 wks
Vaginal Candidiasis/Yeast	<i>Candida</i>	fluconazole 150 mg PO single dose miconazole 2% vag. cream = Monistat 7®: One applicator (5 g) intravag. qhs x 7d
Lice: Head and Pubic (Crabs)	<i>Pediculosis humanus capitis</i> <i>Phthirus pubis</i>	permethrin cream 1%: apply as liquid on to washed hair for 10 min, then rinse. Repeat in 1 wk
Gonorrhea/Chlamydia	<i>N. gonorrhoeae</i> <i>C. trachomatis</i>	cefixime 400 mg PO single dose + azithromycin 1 g PO single dose or doxycycline 100 mg PO bid x 7d
Herpes	Herpes simplex virus	acyclovir 400 mg PO tid x 7-10d valacyclovir 1 g PO bid x 10d famciclovir 250 mg PO tid x5d
Bacterial Vaginosis	Unclear, associated with: <i>Gardnerella vaginalis</i> <i>Mycoplasma hominis</i> <i>Prevotella sp.</i> <i>Atopobium vaginae</i>	metronidazole 500 mg PO bid x 7d metronidazole gel 1 applicator intravag. daily x 5d

Condition	Microorganisms	Antimicrobial
DERMATOLOGIC		
Mastitis	<i>S. aureus</i> <i>S. pyogenes</i>	cloxacillin 500 mg PO qid x 7d cephalexin 500 mg PO qid x 7d
Tinea Cruris/Pedis (Jock Itch/Athlete's Foot)	Trichophyton	clotrimazole 1% cream – apply bid ketoconazole 2% cream – apply bid
Cellulitis (uncomplicated)	Beta-Hemolytic <i>Strep</i> sp. <i>Staphylococcus</i>	1st line: cephalexin 500 mg PO q6h x 10-14d 2nd line: cloxacillin 500 mg PO q6h x 10-14d or clindamycin 300 mg PO q6-8h x 10-14d, total <1.8 g/d
OPHTHALMOLOGY		
Conjunctivitis (viral)	Adenovirus	None Note: very contagious
Conjunctivitis (bacterial)	<i>S. aureus</i> <i>S. pneumoniae</i> <i>E. Coli</i> <i>H. influenzae</i>	sulfacetamide: 1-2 gtts q2-6h x 7-10d gentamicin: 1-2 gtts q4h x 7-10d erythromycin ointment: apply to lid margins bid-qid, M: 3.5 g tube
Blepharitis	Etiology unclear <i>S. aureus</i> <i>S. epidermidis</i>	erythromycin ophthalmic ointment of no proven benefit If associated with rosacea: doxycycline 100 mg PO bid x 14d

*All doses are adult doses unless otherwise specified

*This chart is not all-encompassing and is non-inclusive of special exceptions (i.e. pregnancy, poor renal clearance, etc.)

References

Abuse

Fogarty CT, Burge S, McCord E. Communicating with patients about intimate partner violence: screening and interviewing approaches. *Fam Med* 2002; 34(5): 369-75.
National Center on Elder Abuse at the American Public Human Services Association. National Elder Abuse Incidence Study: http://www.aoa.gov/eldfam/Elder_Rights/Elder_Abuse/AbuseReport_Full.pdf
Wathen CN, MacMillan HL. Interventions for violence against women. *JAMA* 2003;289(5):589-99.

Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes*. 2008;32(suppl 1):S56.
Nield L et al. Dietary advice for treatment of type 2 diabetes mellitus in adults. *Cochrane Database of Systematic Reviews* 2007; Issue 3.
Norris SL et al. Long-term non-pharmacological weight loss interventions for adults with pre-diabetes. *Cochrane Database of Systematic Reviews* 2005; Issue 2.
Saenz A et al. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2005; issue 3.

Diet and Obesity

Calle E, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of US adults. *NEJM* 1999;341(15):1097-1105.
Canada's Food Guide to Healthy Eating. Health Canada. Last updated 2007.
2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. *CMAJ* 10-Apr-07; 176(8): S1-S13.
Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risks, National Institute of Health, National Heart Lung and Blood Institute, Obesity Education Initiative. http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/bmi_dis.htm.
Dansinger ML et al. 2005. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction. *JAMA*, Jan 2005 vol 293(1): 43-53.
Health Canada. Canada's Food Guide to Healthy Eating. Last updated 2005-06-07. http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/fg-rainbow-arc_en_cie_ga_e.html.
Health Canada. Canada's Physical Activity Guide to Healthy Active Living. <http://www.hc-sc.gc.ca/hppb/paguide/main.html>.
Krauss RM, et al. 2000. AHA Dietary Guidelines. Revision 2000: A statement for healthcare professionals from the nutrition committee of the American Heart Association. *Stroke*: 31: 2751-66.
Lichtenstein AH, et al. Diet and lifestyle recommendations revision 2006: A scientific statement from the American Heart Association Nutrition Committee. *Circulation* 2006;114:82-96.

Dyslipidemia, Hypertension and Heart Disease

Canadian Hypertension Education Program. 2009 Canadian Hypertension Education Program recommendations - an annual update. *Can Fam Physician* 2009; 55(7):697-700.
Canadian Hypertension Education Program. 2010 Canadian Hypertension Education Program recommendations for the management of hypertension. *Can J Cardiol* 2010; 26(5): 241-258.
Elmer PJ et al. Effects of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial. *Ann Intern Med* 2006;144(7):485-95.
Farmer JA & Torre-Amione G. Comparative tolerability of the HMG-CoA reductase inhibitors. *Drug Saf* 2000;23(3):197-213.
Genest J, Frohlich J, Fodor G. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the 2003 update. *CMAJ* 2003;169(9):921-924.
Graham DJ et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292(21):2585-90.
Manson JE et al. Estrogen plus progestin and the risk of coronary heart disease. *NEJM* 2003;349(6):523-34.
McPherson R et al. Canadian Cardiovascular Society position statement – Recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. *Can J Cardiol* 2006; 22(11):913-927.
Ontario Drug Therapy Guidelines for Stable Ischemic Heart Disease in Primary Care (2000). Ontario Program for Optimal Therapeutics. Toronto: Queen's Printer of Ontario, pp. 10.
Onusko E. Diagnosing secondary hypertension. *Am Fam Physician* 2003; 67(1):67-74.
Lichtenstein AH, et al. (2006). Diet and lifestyle recommendations revision 2006: A scientific statement from the American Heart Association Nutrition Committee. *Circulation*, 114: 82-96.
Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: Summary of the 2003 update. Reprinted from *CMAJ* 28 October 2003; 169(1): 921-924.

Smoking

- Cahill K, et al. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews* 2008; Issue 3.
- Health Canada. Canadian Tobacco Use Monitoring Survey (CTUMS). Annual Results 2008. http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/ctums-esutc_2008-eng.php
- Hughes JR et al. Antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews* 2007; Issue 1.
- Shroeder SA. What to do with a patient who smoked. *JAMA* 2005; 294(4): 482-7.
- Stead LF et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2008; Issue 1.
- Stead LF et al. Physician advice for smoking cessation. *Cochrane Database of Systematic Reviews* 2008; Issue 2.

Other

- Assendelft WJJ et al. Spinal manipulative therapy for low-back pain. *Cochrane Database of Systematic Reviews* 2004; Issue 1.
- Bagai A, et al. Does this patient have hearing impairment? *JAMA* 2006;295:416-428.
- Beck E, Sieber WJ, Trejo R. Management of cluster headaches. *Am Fam Physician* 2005; 71(4): 717-24.
- Bent S et al. Does this woman have an acute uncomplicated urinary tract infection? *JAMA*. 2002;287(20):2701-10.
- Brown JP, Josse RG. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *CMAJ* 2002;167:S1-S34.
- Burge SK, Schneider FD. Alcohol-related problems: recognition and intervention. *Am Fam Phys* 1999;59(2):361-70, 372.
- Canadian Task Force on Preventive Health Care. The Canadian Guide to Clinical Preventive Health Care. Ottawa: Minister of Supply and Services Canada and <http://www.ctfphc.org>.
- Centor RM et al. (1981). The diagnosis of strep throat in adults in the emergency room. *Med Decis Making*. 1: 239-46.
- Cheung AM, Feig DS, Kapral M, et al. Prevention of osteoporosis and osteoporotic fractures in post-menopausal women: Recommendation statement from the Canadian Task Force on Preventive Health Care. *CMAJ* 2004;170(11):1665-7.
- Comuz J, Guessous I, Farrat B. Fatigue: a practical approach to diagnosis in primary care. *CMAJ* 2006; 174(6): 765-7.
- David AK, et al. *Family Medicine: Principles and Practice*, 6th ed. New York: Springer-Verlag Inc. 2003.
- Derby CA et al. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? *Urology* 2000;56(2):302-6.
- Domino FJ et al. The 5-Minute Clinical Consult 2010, 18th Ed. Lippincott Williams & Wilkins. 2009.
- Ebell MH. Evidence-based diagnosis: a handbook of clinical prediction rules. Springer, 2001.
- Ebell MH. Treating adult women with suspected UTI. *Am Fam Physician* 2006; 73(2): 293-6.
- Edmonds M et al. Exercise therapy for chronic fatigue syndrome. *Cochrane Database of Systematic Reviews* 2004; Issue 3.
- Evans M. Mosby's Family Practice Sourcebook: An Evidence Based Approach to Care, 4th ed., Elsevier Canada, 2006
- Evans M, Bradwejn J, Dunn L (Eds). Guidelines for the Treatment of Anxiety Disorders in Primary Care. Toronto: Queen's Printer of Ontario. 2002: 41.
- Fauci AS et al. Harrison's Principles of Internal Medicine, 17th Ed. McGraw-Hill Professional, 2008.
- Furlan, AD, et al. Acupuncture and dry-needling for low back pain. *Cochrane Database of Systematic Reviews* 2005; Issue 1.
- Health Canada. An advisory committee statement: National Advisory Committee on Immunization – prevention of pertussis in adolescents and adults. Canada communicable disease report 2003; 29:ACS-5, 6.
- Furlan AD et al. Massage for low-back pain. *Cochrane Database of Systematic Reviews* 2008; Issue 4.
- Gilbert DN et al. The Sanford Guide to Antimicrobial Therapy, 39th Ed.. Sperryville, VA: Antimicrobial Therapy, Inc. 2009.
- Health Canada. Natural Health Products Directorate 2004. <http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/>.
- Holbrook AM (Chair) for Ontario Musculoskeletal Therapy Review Panel. Ontario Treatment Guidelines for Osteoarthritis, Rheumatoid Arthritis, and Acute, Musculoskeletal Injury. Toronto: Queen's Printer of Ontario, 2000:13-24.
- Hueston WJ, Mainous AG. Acute bronchitis. *Am Fam Phys* 1998;57:1270-9.
- Hunt P (2001). Motivating Change. *Nursing Standard*, 16(2): 45-52, 54-55.
- Linde K, et al. Echinacea for preventing and treating the common cold. *Cochrane Database of Systemic Reviews* 2006; Issue 1.
- Linde K et al. St John's wort for depression. *Cochrane Database Systematic Reviews*. 2005; Issue 2.
- Low DE, Desrosiers M, McSherry J et al. A practical guide for the diagnosis and treatment of acute sinusitis. *CMAJ* 1997;156:1S.
- Marshall IIR. Zinc for the common cold. *Cochrane Database of Systematic Reviews* 2006; Issue 3.
- McIsaac WJ, White D, Tannenbaum D, Low DE (1998). A clinical score to reduce unnecessary antibiotic use in patients with sore throat. *CMAJ*. 158(1):75-83.
- Montgomery L, Scoville C. What is the best way to evaluate acute diarrhea? *J Fam Pract* 2002; 51(6).
- Mosby's Family Practice Sourcebook: An Evidence Based Approach to Care, edited by Dr M. Evans, 4th ed., Elsevier Canada, 2006: 343-345.
- National Institutes of Health. Herbs at a glance: black cohosh. National Center for Complementary and Alternative Medicine. 2008. <http://nccam.nih.gov/health/blackcohosh/atag glance.htm> Accessed August 23, 2009.
- Osteoporosis Canada. Calcium requirements. 2009. http://www.osteoporosis.ca/index.php/ci_id/5535/la_id/1.htm Accessed August 23, 2009.
- Pampallona S et al. Combined pharmacotherapy and psychological treatment for depression: a systematic review. *Arch Gen Psychiatry*. 2004;61(7):714-9.
- Rambout L et al. Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. *CMAJ*. 2007;177(5):469-79.
- Roelofs PDDM et al. Non-steroidal anti-inflammatory drugs for low back pain. *Cochrane Database of Systematic Reviews* 2008; Issue 1.
- Rowe T et al. Canadian consensus guidelines on Human Papillomavirus – SOGC clinical practice guidelines. *JOGC* 2007; 29(8): Supplement 3.
- Schiller LR. Chronic diarrhea. *Curr Treat Options Gastroenterol* 2005; 8:259-266.
- St. Michael's Hospital. Fasting blood tests – diagnostic laboratories. <http://www.stmichaelshospital.com/programs/labs/fasting.php> Accessed August 23, 2009.
- Swinson RP et al. Clinical practice guidelines: management of anxiety disorders. *Canadian Journal of Psychiatry* 2006; 51, Supplement 2.
- Toward Optimized Practice Program. Guideline for the diagnosis and management of community acquired pneumonia: adult. 2002 (2008 update).
- Toward Optimized Practice Program. Guideline for the diagnosis and management of acute otitis media. 1999 (2008 update).
- Toward Optimized Practice Program. Guideline for the diagnosis and management of acute pharyngitis. 1999 (2008 update).
- Toward Optimized Practice Program. Guideline for the management of acute bronchitis. 2000 (2008 update).
- Toward Optimized Practice Program. Guideline for the treatment of Helicobacter pylori infection in adults. 2000 (2009 update).
- Toward Optimized Practice Program. Use of PSA and the early diagnosis of prostate cancer. 2006 (2009 update).
- Towheed T et al. Glucosamine therapy for treating osteoarthritis. *Cochrane Database of Systematic Reviews* 2005; Issue 2.
- Walsh PC et al. Campbell's Urology, 8th ed. Philadelphia: WB Saunders Co, 1998.
- Wren BG. The benefits of oestrogen following menopause: why hormone replacement therapy should be offered to postmenopausal women. *Med J Aust* 2009; 190(6):321-5.
- Zink T, Chaffin J. Herbal "health" products: What family physicians need to know, *American Family Physician*. 1998. 58(5):1133-1140.
- Wong T & Latham-Carmanico C. Canadian guidelines on sexually transmitted infections. Ottawa: Public Health Agency of Canada 2006 (reviewed 2008).

Notes

Lined area for notes.

Christopher Kandel, David Sussman and Daniel Vilensky, chapter editors

Doreen Ezeife and Nigel Tan, associate editors

Steven Wong, EBM editor

Dr. Gabor Kandel and Dr. David Wong, staff editors

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Differential Diagnosis of Common Presenting Complaints

Table 1. Differential Diagnosis of Common Presenting Complaints

NAUSEA/ VOMITING	With Abdominal Pain		Without Abdominal Pain/Non GI		
	Relieved by Vomiting	Not Relieved by Vomiting	Headache/Dizziness	No other Symptoms	
	Gastric Outlet Obstruction Small Bowel Obstruction GERD	Gallbladder disease Pancreatitis Myocardial Infarction Hepatitis	Cerebral tumour Migraine Vestibular Increased ICP	Drugs Uremia Pregnancy Metabolic (e.g. hypercalcemia) Gastroparesis (e.g. diabetes) Ketoacidosis	
DYSPHAGIA	Mechanical (Solids)	Motility (Solids and Liquids)	Other		
	Stricture /Cancer Eosinophilic esophagitis Extrinsic compression Schatzki ring/esophageal web Zenker's diverticulum	Achalasia Diffuse esophageal spasm Scleroderma	Foreign Body		
ODYNOPHAGIA	Infection	Inflammation/Ulceration	Drugs	Other	
	Candida Herpes CMV (common only in those who are immunosuppressed)	Caustic damage	Quinidine Iron Vitamin C Antibiotics (e.g. tetracycline)	Radiation	
ABDOMINAL DISTENTION	Fluid		Flatulence	Feces	Other
	Portal HTN	Normal Portal Pressure			
	Cirrhosis Cardiac Failure Hepatic Vein Thrombosis	Cancer esp. ovarian Pancreatitis TB	Functional Bowel Disease Fibre Lactose Chewing gum (e.g. sorbitol, mannitol)	Constipation Colonic obstruction Dysmotility	Pregnancy (fetus) Obesity (fat) Blood Large Tumours (fatal growth)
ACUTE ABDOMINAL PAIN	Upper/Mid-Abdomen	Lower Abdomen			
	Gastroenteritis Cholecystitis Perforated Peptic Ulcer Pancreatitis Small bowel obstruction Mesenteric ischemia Ruptured aortic aneurysm	Gastroenteritis Appendicitis Diverticulitis Crohn's disease Pelvic inflammatory disease Ectopic pregnancy			
CHRONIC/ RECURRENT ABDOMINAL PAIN	Inflammatory	Neoplastic/Vascular	Toxin	Other	
	PUD Biliary colic IBD Chronic pancreatitis	Recurrent bowel obstruction Mesenteric Ischemia Sickle cell anemia	Lead poisoning	Mittelschmerz Endometriosis Porphyria IBS Radiculopathy	
ACUTE DIARRHEA	Invasive	Non-invasive			
	Bacterial <i>Salmonella</i> <i>Campylobacter</i> <i>C. Difficile</i> <i>E. coli</i> (EHEC O157:H7) <i>Shigella</i> <i>Yersinia</i> Protozoal <i>E. histolytica</i> (amebiasis) Strongyloides	Bacterial <i>Saphylococcus aureus</i> <i>B. cereus</i> <i>C. perfringens</i> <i>Vibrio cholera</i> Protozoal <i>Giardia lamblia</i>		Viral Rotavirus Norwalk Cytomegalovirus Drugs Antibiotics Laxatives (Magnesium) Antacids Colchicine Many others	
CHRONIC DIARRHEA	Inflammatory	Secretory	Steatorrhea	Osmotic	
(a) Organic	IBD Ischemic Bowel	Stimulant laxatives Ileal resection (bile salts) Large, villous adenoma Zollinger-Ellison (ZE) Carcinoid Addison's disease VIPoma Parasites	<i>Giardia lamblia</i> Celiac sprue Chronic pancreatitis Diabetes Mellitus	Drugs/Laxatives Lactose intolerance Chewing gum (e.g. sorbitol, mannitol)	
(b) Functional	IBS Constipation (overflow diarrhea) Anal sphincter dysfunction				



Commonly Forgotten Causes of Vomiting

Drugs
Uremia
CNS Disease
Pregnancy



Differential Diagnosis of Abdominal Distention

6 F's
• Fat
• Feces
• Fetus
• Flatus
• Fluid
• Fatal Growth



Acute Upper Abdominal Pain

Remember to consider chest source, e.g. myocardial infarction, pneumonia, dissecting aneurysm.



Intermittent abdominal pain precipitated by eating: think of obstruction (gastric outlet, small bowel); pancreatitis; ischemic bowel.



Obscure But Treatable Causes of Abdominal Pain

Porphyria
Angioedema
Familial Mediterranean Fever
Vasculitis (e.g. polyarteritis nodosa)



Watch out for IBD with bloody diarrhea.

Table 1. Differential Diagnosis of Common Presenting Complaints (continued)

CONSTIPATION			
		Colorectal Cancer Stricture Extrinsic Compression Anal disease Rectocele	Medications (narcotics, antidepressants, calcium channel blockers) Metabolic (diabetes, thyroid, hypercalcemia) Neurological (Parkinson's, multiple sclerosis, stroke) Collagen Vascular Disease (scleroderma, dermatomyositis)
DYSPEPSIA	Common	Uncommon	Rare
	Functional dyspepsia Drug side effect Peptic ulcer GERD	Angina Crohn's disease Cancer Gallstones Aerophagia	<i>Giardia lamblia</i> Malabsorption (celiac sprue)
UPPER GI BLEED	Common	Uncommon	Rare
	Ulcers (<i>H. pylori</i> , ASA, NSAIDs) Esophageal varices Mallory-Weiss tears Erosive esophagitis Erosive gastritis	Tumours Arteriovenous malformation Dieulafoy's lesion Gastric antral vascular ectasia Portal hypertensive gastropathy	Aorto-enteric fistulas Hemobilia
LOWER GI BLEED	Common	Uncommon	Rare
	Diverticulosis Ischemia Angiodysplasia (elderly) Infectious Anorectal (hemorrhoids, fissure, ulcer)	Upper GI bleed Post-polypectomy Radiation colitis IBD	Intussusception Vasculitides Stercoral Ulcer Coagulopathies

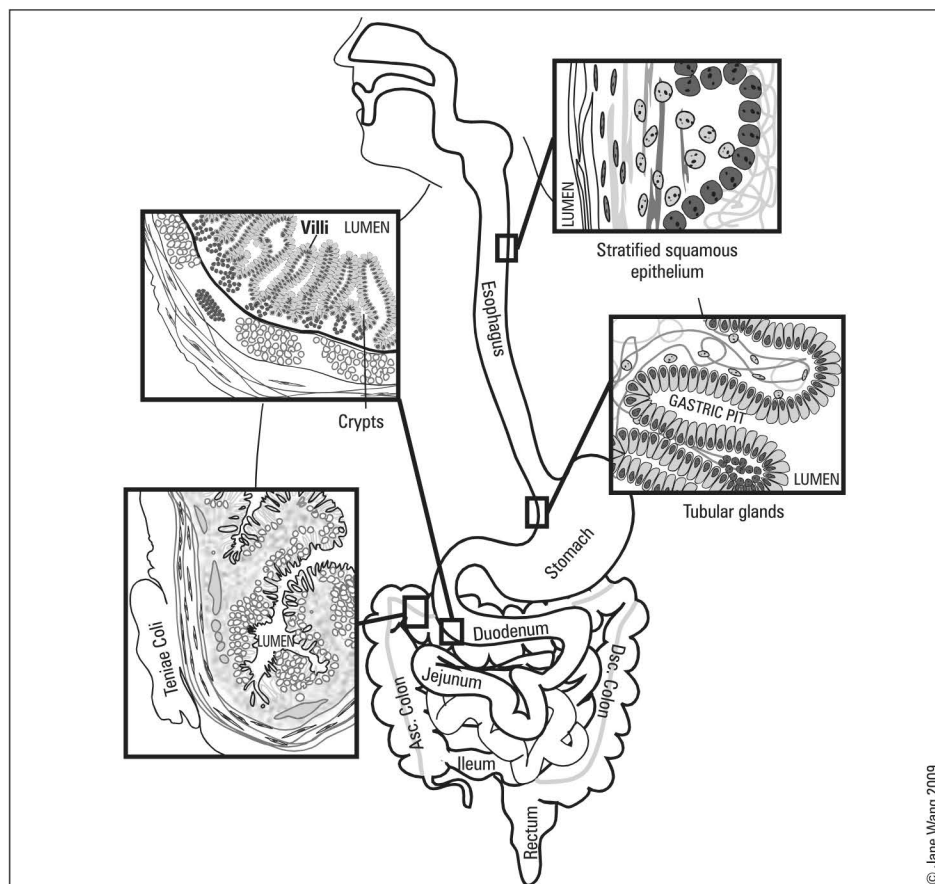


Most common cause of constipation is inadequate fibre or fluid intake.

Anatomy Review

Overview of Gastrointestinal Tract

- the gastrointestinal tract runs from mouth to anus ("gum to bum")



Retroperitoneal Structures

SAD PUCKER

Suprarenal glands (aka the adrenal glands)
Aorta/IVC
Duodenum (second to fourth segments)
Pancreas (tail is intraperitoneal)
Ureters
Colon (only the ascending and descending branches)
Kidneys
Esophagus
Rectum

Figure 1. Overview of Gastrointestinal Tract

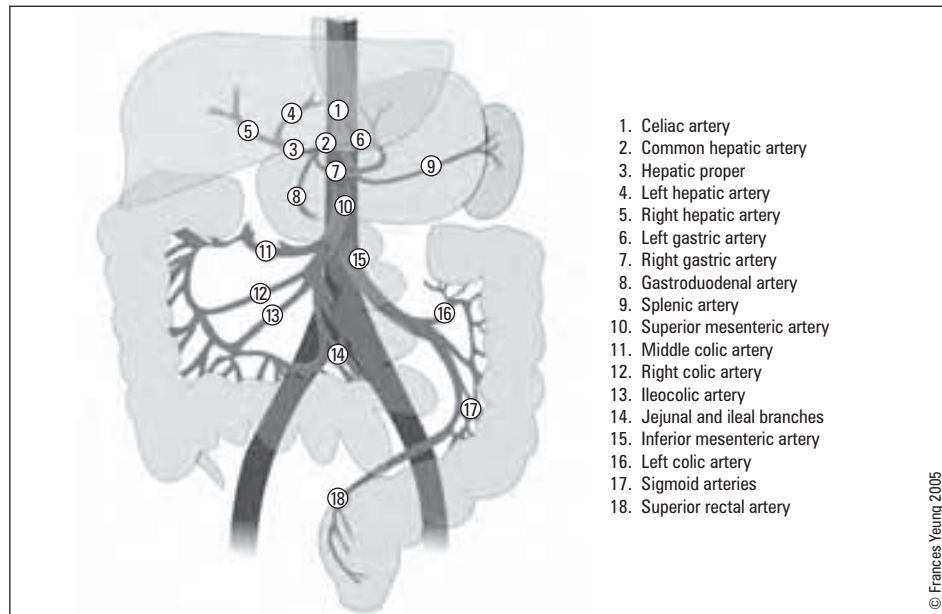


Figure 2. Arterial Supply of Gastrointestinal Tract

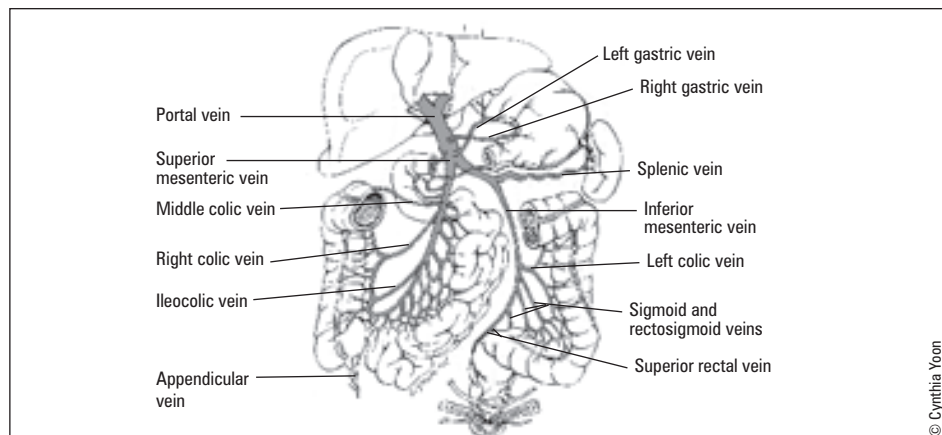


Figure 3. Anatomy of Portal Venous System

Table 2. Summary of Gastrointestinal Tract Structure and Function

Organ	Function	Blood Supply	Innervation	Histology and Structural Features
Esophagus	<ul style="list-style-type: none"> Muscular tube approximately 25 cm long with a diameter of 2 cm Extends from pharynx to the stomach 	<ul style="list-style-type: none"> Arterial: left gastric artery and left inferior phrenic artery Venous: left gastric vein → portal venous system Esophageal veins → azygos vein 	<ul style="list-style-type: none"> Vagal trunks which become the anterior and posterior gastric nerves Thoracic sympathetic trunks via the greater splanchnic nerves 	<ul style="list-style-type: none"> Mucosa: stratified squamous epithelium Submucosa: connective tissue, lymphocytes, plasma cells, nerve cells Muscularis propria: inner circular, outer longitudinal muscle Muscle: upper 1/3 striated muscle, lower 1/3 smooth muscle, separated by transition zone comprised of both
Stomach	<ul style="list-style-type: none"> Chief function is enzymatic digestion Converts mass of food into semiliquid mixture called chyme 	<ul style="list-style-type: none"> Lesser curvature: <ul style="list-style-type: none"> Right and left gastric arteries (from celiac trunk) Greater curvature: <ul style="list-style-type: none"> Right and left gastromental arteries Fundus: short and posterior gastric arteries (from the splenic artery) 	<ul style="list-style-type: none"> Parasympathetic innervation via vagus nerve Sympathetic supply via celiac plexus (from T6-T9) 	<ul style="list-style-type: none"> 4 parts: <ul style="list-style-type: none"> Cardia Fundus Body Pylorus
Duodenum	<ul style="list-style-type: none"> Neutralizes acidic components entering from stomach via secretin and bicarbonate secretion Site of stimulation of bile secretion via CCK release 	<ul style="list-style-type: none"> Branches of celiac and superior mesenteric artery (SMA) 	<ul style="list-style-type: none"> Parasympathetic innervation from the vagus Sympathetic innervations from the greater and lesser splanchnic nerves 	<ul style="list-style-type: none"> 4 parts <ul style="list-style-type: none"> Superior (5 cm) Descending (7-10 cm) Horizontal (6-8 cm) Ascending (5 cm) 1st part is intraperitoneal; rest is retroperitoneal

Table 2. Summary of Gastrointestinal Tract Structure and Function (continued)

Organ	Function	Blood Supply	Innervation	Histology and Structural Features
Jejunum	<ul style="list-style-type: none"> Absorption of salt, water and nutrients (protein, carbohydrates, fat, folic acid, vit B, C, and vit A, D, E, K) 	<ul style="list-style-type: none"> Superior mesenteric artery 	<ul style="list-style-type: none"> Sympathetic fibres (originate from T8-T10) Parasympathetic fibers from the posterior vagal trunk 	<ul style="list-style-type: none"> Deep red colour 2-4 cm in thickness Has a thick and heavy wall Plicae circulares are large, tall and closely packed Has long vasa recta Has little fat in mesentery Has few Peyer Patches
Ileum	<ul style="list-style-type: none"> Absorption of salt, water and nutrients, soluble vitamins (incl. vit B₁₂), bile salts (entero-hepatic circulation) 	<ul style="list-style-type: none"> Superior mesenteric artery 	<ul style="list-style-type: none"> Same as jejunum 	<ul style="list-style-type: none"> When compared to jejunum: <ul style="list-style-type: none"> Paler pink colour 2-3 cm in thickness Has a thin and light wall Plicae circulares are small and sparse Contains more fat in mesentery than jejunum Has many Peyer patches
Large Bowel	<ul style="list-style-type: none"> Absorption of water (5-10% of total water) Bacteria: further digestion of chyme and metabolism of undigested CHO to short chain fatty acids Formation and storage of feces 	<ul style="list-style-type: none"> Branches of superior and inferior mesenteric artery 	<ul style="list-style-type: none"> Parasympathetic innervation from the vagus Sympathetic innervations from the greater and lesser splanchnic nerves 	<ul style="list-style-type: none"> Consists of cecum, colon (ascending, transverse, descending and sigmoid), rectum and anal canal Features include <ul style="list-style-type: none"> Teniae coli Haustra Omental appendices
Liver	<ul style="list-style-type: none"> Glucose homeostasis Plasma protein synthesis Lipid and lipoprotein synthesis Bile acid synthesis and secretion Vitamin A, D, E, K, B₁₂ storage Biotransformation, detoxification Excretion of endogenous and exogenous compounds 	<ul style="list-style-type: none"> 2 sources <ul style="list-style-type: none"> Portal vein (75-80%) Hepatic artery (20-25%) 	<ul style="list-style-type: none"> Sympathetic fibers from the celiac plexus Parasympathetic fibers from the anterior and posterior vagal trunks 	<ul style="list-style-type: none"> Largest internal organ Composed of 4 lobes (left, right, caudate, quadrate) and divided into 8 segments
Biliary Tract	<ul style="list-style-type: none"> Gallbladder functions to store and release bile that is produced in the liver Bile is used to emulsify fat and is composed of cholesterol, lecithin, bile acids and bilirubin Cholecystokinin stimulates gallbladder emptying while trypsin and chymotrypsin inhibit bile release 	<ul style="list-style-type: none"> Gallbladder blood supply: cystic artery 	<ul style="list-style-type: none"> Celiac nerve plexus [carry sympathetic and visceral (pain) afferents] Parasympathetic from the vagus Somatic afferent fibers: right phrenic nerve 	<ul style="list-style-type: none"> Consists of the hepatic ducts (intrahepatic, left, right and common), gallbladder, cystic duct, common bile duct and ampulla of Vater
Pancreas	<ul style="list-style-type: none"> Endocrine function: Islets of Langerhans produce glucagon, insulin and somatostatin (from the alpha, beta and delta cells, respectively) Exocrine function: digestive enzymes are produced including amylase, lipase, trypsin, chymotrypsin and carboxypeptidase 	<ul style="list-style-type: none"> Anterior/posterior superior pancreaticoduodenal artery (from the celiac trunk) Anterior/posterior inferior pancreaticoduodenal artery (from the superior mesenteric artery) Dorsal pancreatic artery (from the splenic artery) Pancreatic veins drain into the portal, splenic and superior mesenteric veins 	<ul style="list-style-type: none"> Vagus and abdominopelvic splanchnic nerves 	<ul style="list-style-type: none"> Generally divided into 4 parts: head (includes uncinate process), neck, body, tail



Remember: Only ileum, not jejunum, can absorb vitamin B₁₂ and bile acids

Esophagus

Dysphagia

Definition

- difficulty swallowing, sensation of food “sticking” after swallowing



Key Questions in Dysphagia

- Difficulty in starting swallowing?
- Associated symptoms? (regurgitation, change in voice pitch, weight loss)
- Solids, liquids or both
- Intermittent or progressive
- History of heartburn
- Change in eating habits/diet



Odynophagia = Pain on swallowing

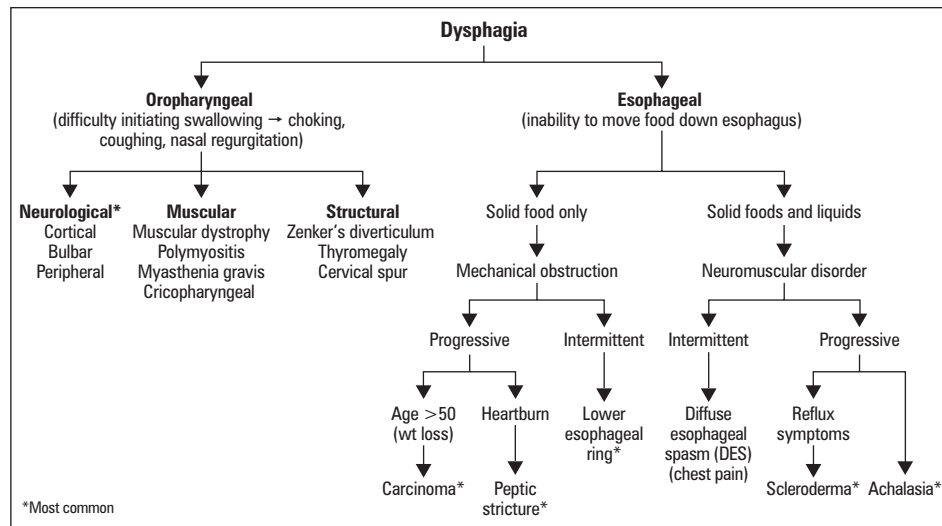


Figure 4. Approach to Dysphagia

Dyspepsia

Definition

- intermittent epigastric discomfort, characteristically develops after eating
- organic disease most likely if age over 55, associated symptoms, taking medications (especially NSAIDs)



Gastroesophageal Reflux Disease (GERD)

Definition

- reflux of gastric contents, especially acid, aborally (toward the mouth) rather than distally into duodenum

Etiology

- inappropriate transient relaxations of lower esophageal sphincter (LES) – most common
- low basal LES tone (especially in scleroderma)
- contributing factors include: delayed esophageal clearance, delayed gastric emptying, increased intra-abdominal pressure
- acid hypersecretion (rare) – Zollinger-Ellison syndrome (gastrin-secreting tumour)
- hiatus hernia worsens reflux, does not cause it (see [General Surgery](#), GS21)

Clinical Features

- “heartburn” (pyrosis) and acid regurgitation (together are 80% sensitive and specific for reflux)
- ± bitter regurgitation, water brash; sensation of a lump in the throat; frequent belching



Key Questions to Ask

Dysphagia
Weight Loss



Foods/substances that Aggravate GERD Symptoms

EtOH
Caffeine
Tobacco
Fatty/fried foods
Chocolate
Peppermint
Spicy foods
Citrus fruit juices

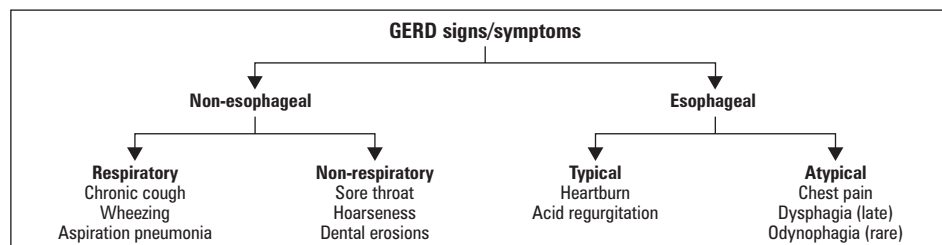


Figure 5. Signs and Symptoms of GERD

Investigations

- usually a clinical diagnosis based on symptom history and relief following a trial of pharmacotherapy (proton pump inhibitor (PPI): symptom relief 80% sensitive for reflux)
- gastroscopy indications:
 - rule out conditions that mimic reflux (e.g. cancer, peptic ulcer, infective esophagitis)
 - distinguish between esophagitis (indicating aggressive treatment) and non-esophagitis reflux disease (NERD – sole goal of treatment is symptom relief)
 - diagnose Barrett's esophagus (requires endoscopic surveillance for cancer)
- esophageal manometry
 - may be done to diagnose abnormal peristalsis and/or decreased LES tone, but cannot detect presence of reflux; indicated before surgical fundoplication to ensure esophagus functional
 - surgical fundoplication more likely to be successful if lower esophageal pressure is diminished; less likely to be successful if abnormal peristalsis
- barium swallow: to assess presence of strictures
- 24-hour pH monitoring: most accurate test but rarely required
 - most useful if PPIs not helpful

Management

- PPIs are most effective therapy, usually need to be continued on maintenance therapy
- on-demand: antacids (MgOH, AlOH, alginate), H₂-blockers or PPIs can be used for NERD
- diet helps symptoms, not the disease; only beneficial lifestyle changes are weight loss (if obese) and elevating the head of bed (if nocturnal symptoms)

Complications

- esophageal stricture disease – scarring can lead to dysphagia (solids)
- ulcer
- bleeding
- Barrett's esophagus (see below) and esophageal adenocarcinoma (0.4% risk per year) – mandates surveillance gastroscopy q2-4yrs

Barrett's Esophagus

Definition

- metaplasia of normal squamous epithelium to abnormal columnar epithelium containing intestinal metaplasia and resulting displacement of the squamocolumnar junction proximal to the gastroesophageal junction

Etiology

- thought to be acquired via long-standing GERD and consequent damage to squamous epithelium

Epidemiology

- in North America and Western Europe, 0.5-2.0% of adults are thought to have Barrett's Esophagus (BE)
- up to 10% of GERD patients will have already developed BE by the time they seek medical attention
- more common in males, >50 yrs, Caucasians and smokers

Pathophysiology

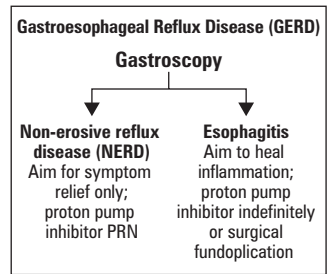
- endoscopy shows erythematous epithelium in distal esophagus; diagnosis of BE relies on biopsy demonstrating the presence of specialized intestinal epithelium of any length within the esophagus
- BE predisposes to premalignant changes in abnormal columnar epithelium, characterized as low- or high-grade dysplasia

Significance

- rate of malignant transformation is approximately 0.4% per year for all BE patients prior to dysplasia
- risk of malignant transformation in high-grade dysplasia is significantly higher; studies have reported a 32-59% transformation rate over 5-8 years of surveillance
- gastric acid secretion increased more often than in reflux without Barrett's

Management

- surveillance gastroscopy with esophageal mucosal biopsy one year after initial diagnosis then every 2-3 years to detect neoplasia
- if dysplasia develops, can be treated non-surgically with endoscopic ablation, endoscopic mucosal resection, radiofrequency, photodynamic therapy or surgery
- acid suppressive therapy with high-dose PPI indefinitely; provides symptom relief
 - may decrease rate of progression to cancer



Esophageal damage from reflux is most severe at first gastroscopy, therefore necessary only once for patients with NERD.



Up to 25% of patients with Barrett's Esophagus do not report symptoms of GERD.

Eosinophilic Esophagitis

Definition

- inflammatory condition with prominence of eosinophils on esophageal biopsy
- most commonly found in children, but increasingly recognized in adults

Etiology

- unknown; may be an “allergic” disorder in children
- cytokines cause edema and fibrosis

Clinical Features

- dysphagia (solids); history often dates back to childhood
- first presentation may be to ER with food bolus impaction

Investigations

- endoscopy may reveal multiple rings or “crepe-paper” appearance
- biopsy necessary to confirm diagnosis

Management

- corticosteroid (e.g. fluticasone) spray – swallowed not inhaled
- leukotriene B4 inhibitors (e.g. Montelukast)

Complications

- progressive narrowing
- increased risk of perforation with bougienage



Esophageal Motor Disorders

Symptoms

- dysphagia with solids and liquids
- chest pain (in some disorders)

Diagnosis

- esophageal motility study (esophageal manometry)
- barium swallow sometimes helpful

Causes (Table 3)

- idiopathic
- achalasia (painless)
- scleroderma (painless)
- diabetes
- diffuse esophageal spasm (DES) – rare, can be difficult to diagnose because intermittent

Table 3. Esophageal Motor Disorders

Disorder	Achalasia	Scleroderma	Diffuse Esophageal Spasm (DES)
Definition	<ul style="list-style-type: none"> • Failure of smooth muscle relaxation at LES • Progressive loss of peristaltic function 	<ul style="list-style-type: none"> • See <u>Rheumatology</u>, RH11 • Disease of collagen 	<ul style="list-style-type: none"> • Normal peristalsis interspersed with frequent, repetitive, spontaneous, high pressure, non-peristaltic waves (tertiary peristalsis)
Etiology	<ul style="list-style-type: none"> • Usually idiopathic • Incomplete relaxation of LES with swallowing • High LES resting pressure in most (if 2° to cancer, considered pseudo-achalasia) • Chagas disease (<i>T. cruzi</i>) 	<ul style="list-style-type: none"> • Dysphagia: can be due to reflux or dysmotility, usually both 	<ul style="list-style-type: none"> • Unknown
Pathophysiology	<ul style="list-style-type: none"> • Unknown (increased impaired inhibition related to decreased NO release) 	<ul style="list-style-type: none"> • Blood vessel damage → intramural neuronal dysfunction → distal esophageal muscle weakening → aperistalsis and loss of LES tone → reflux → stricture → dysphagia 	<ul style="list-style-type: none"> • Unknown

Table 3. Esophageal Motor Disorders (continued)

Disorder	Achalasia	Scleroderma	Diffuse Esophageal Spasm (DES)
Diagnosis	<ul style="list-style-type: none"> Chest x-ray: no air in stomach, with dilated esophagus Barium studies: esophagus terminates in narrowing at the sphincter, giving a "bird's beak" appearance Endoscopy to r/o malignancy Motility study for definitive diagnosis 	<ul style="list-style-type: none"> Clinical features of scleroderma Manometry: decreased pressure in LES, decreased peristalsis in body of esophagus 	<ul style="list-style-type: none"> Barium x-ray: "Corkscrew pattern"
Treatment	<ul style="list-style-type: none"> Dilatation of LES with balloon, \pm GERD prophylaxis, 50% good response, can repeat, risk of perforation (5%) Injection of botulinum toxin into LES (temporary) Surgery (myomectomy) 	<ul style="list-style-type: none"> Medical: aggressive GERD therapy (PPIs bid) Surgery: anti-reflux surgery (gastroplasty, last resort) 	<ul style="list-style-type: none"> Reassurance not cardiac pain Medical: nitrates, calcium channel blockers, anticholinergics have variable benefit Surgical: long esophageal myotomy if unresponsive to above treatment (rarely helpful); balloon dilatation

Esophageal Diverticula

Definition

- outpouchings of one or more layers of GI tract

Clinical Features

- commonly associated with motility disorders
- dysphagia, regurgitation, retrosternal pain, intermittent vomiting, may be asymptomatic

Classification

- classified according to location
 - pharyngoesophageal (Zenker's) diverticulum
 - most frequent form of esophageal diverticulum
 - posterior pharyngeal outpouching most often on the left side, above cricopharyngeal muscle and below the inferior pharyngeal constrictor muscle
 - symptoms: dysphagia, regurgitation of undigested food, halitosis
 - treatment: endoscopic or surgical myotomy of cricopharyngeal muscle \pm surgical excision of sac
 - mid-esophageal diverticulum
 - secondary to mediastinal inflammation, motor disorders
 - usually asymptomatic; no treatment required
 - just proximal to LES (pulsatile type)
 - usually associated with motor disorders
 - usually asymptomatic; no treatment required

Peptic Stricture (From Esophagitis)

- presents as intermittent or progressive dysphagia in face of reflux symptoms, but reflux symptoms may disappear with progression
- diagnose with barium study or endoscopy

Treatment

- endoscopic dilatation and indefinite PPI
- anti-reflux surgery if above unsuccessful

Esophageal Cancer

- see General Surgery, GS14

Webs and Rings

- web = partial occlusion (upper esophagus)
- ring = circumferential narrowing (lower esophagus)

Clinical Features

- asymptomatic with lumen diameter >12 mm, provided peristalsis is normal
- dysphagia with large food boluses
- Plummer-Vinson or Patterson-Kelly syndrome
 - upper esophageal web with iron deficiency, plus cheilosis (dry scaling and fissuring of the lips) and koilonychia (concave outer nail surface)
 - usually in middle-aged females (>40 years)
 - elevated risk of hypopharyngeal carcinoma
- Schatzki's ring
 - mucosal ring at squamo-columnar junction above a hiatus hernia
 - causes intermittent dysphagia with solids
 - treatment involves disrupting ring with endoscopic bougie

Infectious Esophagitis

Definition

- severe mucosal inflammation and ulceration as a result of viral or fungal infection

Risk Factors

- diabetes
- malignancy (chemotherapeutic agents)
- immunocompromised states

Symptoms

- characteristically odynophagia, less often dysphagia
- diagnosis is via endoscopic visualization and biopsy

Treatment



- *Candida* (most common): nystatin swish and swallow, ketoconazole, fluconazole
- Herpes (second most common): often self-limiting; acyclovir, vancyclovir, famciclovir
- CMV: IV ganciclovir, famciclovir



Stomach and Duodenum

Gastritis

Definition

- defined histologically: inflammation of the stomach mucosa

Etiology

- most common causes (see Table 4)
 - *Helicobacter pylori* infection
 - drugs: NSAIDs
 - physiological stress-related mucosal changes (in ICU)
 - other (rare): granulomatous, lymphocytic, eosinophilic, infectious (TB, syphilis, CMV)
- Crohn's disease

Clinical Features

- only erosive gastritis presents with symptoms (bleeding)
- non-erosive gastritis is asymptomatic
- erosions may be present on endoscopy

Management

- determined by underlying etiology (see below)

Table 4. Updated Sydney Classification of Gastritis

Type	Common Etiology
Non-atrophic Multifocal	<i>Helicobacter pylori</i>
Lymphocytic	Celiac disease
Eosinophilic	Allergy
Granulomatous	TB, syphilis, Crohn's disease, sarcoidosis

Gastric Acid Secretion

Stomach

- primary function is mechanical grinding of food facilitating early enzymatic digestion into chyme and propulsion into duodenum

Table 5. Cells of the Gastric Mucosa

Cell Type	Secretory Product	Important Notes
Parietal cells	Gastric acid (HCl) Intrinsic factor	Stimulated by histamine, ACh, gastrin
Chief cells	Pepsinogen	Stimulated by vagal input and local acid
G-cells	Gastrin	Stimulates H ⁺ production from parietal cells
Superficial epithelial cells	Mucus, HCO ₃ ⁻	Protect gastric mucosa

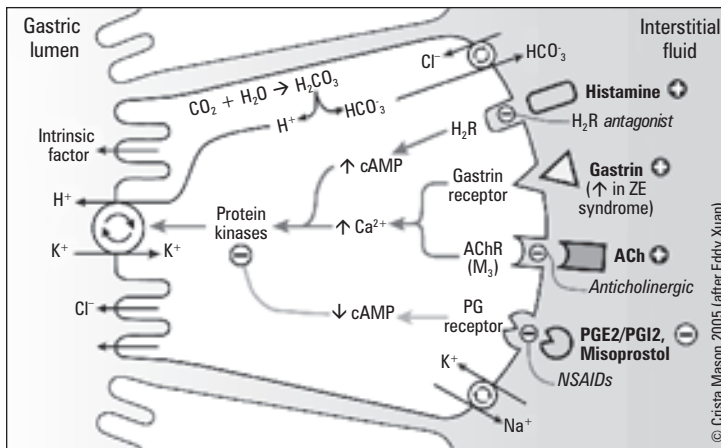


Figure 6. Stimulation of H⁺ Secretion from the Parietal Cell

Peptic Ulcer Disease (PUD)



Definition

- erosion (superficial to the muscularis mucosa, thus no scarring) or ulcer (penetrates the muscularis mucosa and can result in scarring)

Etiology

Table 6. Etiology of Peptic Ulcer Disease

	Duodenal	Gastric
<i>H. pylori</i> infection	90%	60%
NSAIDs	7%	35%
Physiologic stress-induced	<3%	<5%
Zollinger-Ellison (ZE) syndrome	<1%	<1%



Gastric vs. Duodenal Ulcers
Gastric ulcers must always be biopsied to rule out malignancies. Duodenal ulcers are rarely malignant.

- NSAID negative, *H. pylori* negative ulcers becoming more commonly recognized
- others: CMV, ischemic, idiopathic
- alcohol: damages gastric mucosa but only rarely causes ulcers
- peptic ulcer associated with cirrhosis of liver, COPD, chronic renal failure

Clinical Features

- dyspepsia: most common presenting symptom
 - only 20% of patients with dyspepsia have ulcers
- may present with complications
 - bleeding 10% (severe if from gastroduodenal artery); see *Bleeding Peptic Ulcer*, G27
 - perforation 2% (usually anterior ulcers)
 - gastric outlet obstruction 2%
 - penetration (posterior) 2%; may also cause pancreatitis

- duodenal ulcers present with 6 classical features:
 - epigastric pain; may localize to tip of xiphoid
 - burning
 - develops 1-3 hours after meals
 - relieved by eating and antacids
 - interrupts sleep
 - periodicity (tends to occur in clusters over weeks with subsequent periods of remission)
- gastric ulcers have more atypical symptoms; a biopsy is necessary to exclude malignancy

Investigations

- endoscopy (most accurate)
- upper GI series
- *H. pylori* tests (see Table 7)
- fasting serum gastrin measurement if Zollinger-Ellison (ZE) syndrome suspected

Treatment

- specific management depends on etiology; refer to *H. pylori*, NSAID and Stress-Induced Ulceration sections (see below)
- eradicate *H. pylori* if present, chief advantage is to lower ulcer recurrence rate
- stop NSAIDs if possible
- start PPI: inhibits parietal cell H^+/K^+ -ATPase pump which secretes acid
 - heals most ulcers, even if NSAIDs are continued
- other meds (e.g. histamine H_2 -antagonists) less effective
- discontinue tobacco
- no diet modifications required but some people have fewer symptoms if they avoid caffeine, alcohol and spices



Approach to PUD

1. Stop NSAIDs
2. Acid neutralization
3. *H. pylori* eradication
4. Quit smoking



Cigarette Smoking and PUD

- Increased risk of ulcer
- Increased risk of complications
- Increased chance of death from ulcer
- Impairs healing

H. pylori-Induced Ulceration

Pathophysiology

- *H. pylori*: Gram-negative flagellated rod that resides on but does not invade the gastric mucosa
- acid secreted by parietal cell (stimulated by vagal acetylcholine, gastrin, histamine) necessary for most ulcers
- mucosal defenses moderated by PGE_2 and blood flow, mucus, etc.
- theories of how *H. pylori* causes ulcers:
 - toxin production: causes gastric mucosal inflammation and necrosis
 - interference with acid regulation: *H. pylori* blocks G cells in antrum from sensing luminal acid → increased serum gastrin → increased gastric acid → ulcer

Epidemiology

- *H. pylori* is found in about 20% of all Canadians
 - highest prevalence in those raised during 1930s
- infection most commonly acquired in childhood, presumably by fecal-oral route
- high prevalence in developing countries, low socioeconomic status (poor sanitation and crowding)

Symptoms

- non-erosive gastritis in 100% of patients but this does not cause symptoms
- peptic ulcer in 15% of patients, gastric malignancy (cancer and mucosal associated lymphomatous tissue lymphoma [MALT lymphoma] in 0.5% of patients)
- most are asymptomatic but still worthwhile eradicating to lower future risk of peptic ulcer/ gastric malignancy and prevent spread to others (mostly children <5 years of age)

Investigations

Table 7. Diagnosis of *H. pylori* Infection

Test	Sensitivity	Specificity	Comments
Non-invasive Tests			
Urea breath test	90-100%	89-100%	Affected by PPI therapy (false negatives)
Serology	88-99%	89-95%	Can remain positive after treatment
Invasive Tests (require endoscopy)			
Histology	93-99%	95-99%	Gold standard; affected by PPI therapy (false negatives)
Rapid urease test (on biopsy)	89-98%	93-100%	Rapid
Microbiology culture	98%	95-100%	Research only

Treatment: *H. pylori* Eradication

- triple therapy for 7-14 days (Hp-Pac®): PPI BID + amoxicillin 1 g BID + clarithromycin 500 mg BID
 - 90% success rate
- quadruple therapy for 10-14 days: PPI BID + tripotassium dicitratobismuthate 120 mg qid + tetracycline 500 mg qid + metronidazole 250 mg qid
 - only recommended as first line therapy if resistance to clarithromycin or metronidazole is high, or in patients with recent or repeated exposure to these drugs
- sequential therapy
 - days 1-5: PPI bid + amoxicillin 1 g BID
 - days 6-10: PPI bid + clarithromycin 500 mg BID + metronidazole or tinidazole 500 mg BID
- 5-15% of cases are resistant to all known therapies

NSAID-Induced Ulceration

- NSAIDs cause gastric mucosal petechiae in virtually all users, erosions in most users, ulcers in some users (25%)
 - erosions bleed, but usually only ulcers cause significant clinical problems
- most NSAID ulcers are clinically silent: dyspepsia is as common in patients with ulcers as in patients without ulcers; NSAID-induced ulcers characteristically present with complications (bleeding, perforation, obstruction)
- NSAIDs more commonly cause gastric ulcers than duodenal ulcers
- may exacerbate underlying duodenal ulcer disease

Pathophysiology

- direct: petechiae and erosions are due to local effect of drug on gastric mucosa
- indirect: systemic NSAID effect
 - NSAIDs inhibit mucosal cyclooxygenase, leading to decreased synthesis of protective prostaglandins, thus leading to ulcers

Risk Factors For NSAID Causing Peptic Ulcer

- age
- previous peptic ulcers/UGIB
- high dose of NSAID/multiple NSAIDs being taken
- concomitant corticosteroid use
- concomitant cardiovascular disease/other significant diseases

Treatment

- prophylactic cytoprotective therapy (PPI) is recommended if any of the above risk factors exist concomitantly with ASA/NSAID use
- lower NSAID dose, or stop all together and replace with acetaminophen
- combine NSAID with PPI or misoprostol
- enteric coating of aspirin (ECASA) provides minor benefit since this decreases incidence of erosion, not incidence of ulceration



If at high risk for development of ulcers, prophylaxis with PPI indicated

The David Y Graham Lecture: Use of Nonsteroidal Antiinflammatory Drugs (NSAID) in a COX-2 Restricted Environment

Am J Gastroenterol 2008; 103:221-227
This short article reviews the current understanding of NSAID risks, emphasizing (1) with the possible exception of naproxen, all NSAIDs increase cardiovascular/cerebrovascular risk, especially the COX-2 specific inhibitors (2) low-dose aspirin, now used widely to decrease these risks, increases the likelihood of upper GI tract bleeding and may not abrogate the cardiovascular risk of NSAIDs (3) clopidogrel is no safer than aspirin in patients with high risk of upper GI tract bleeding (4) add a proton pump inhibitor to NSAID if there is an increased risk of upper GI events.

Stress-Induced Ulceration**Definition**

- ulceration or erosion in the upper GI tract of ill patients, usually in ICU
- lesions most commonly in fundus of stomach

Pathophysiology

- unclear: likely involves ischemia; may occur with CNS disease, acid hypersecretion
- physiological stress (e.g. fever, severe illness, complex post-op course) causes ulcers and erosions

Risk Factors

- mechanical ventilation
- anti-coagulation
- multi-organ failure
- septicemia
- severe surgery/trauma
- CNS injury ("Cushing's ulcers")
- burns involving more than 35% of body surface

Clinical Features

- UGIB (see *Upper Gastrointestinal Bleeding*, G26)
- painless

Treatment

- prophylaxis with gastric acid suppressants (H_2 -blockers or PPI) decreases risk of UGIB, but may increase risk of pneumonia
- treatment same as for bleeding peptic ulcer but often less successful

Gastric Cancer

- see *General Surgery*, GS17

Small and Large Bowel**Classification of Diarrhea****Definition**

- clinically, diarrhea defined as stools that are looser and/or more frequent than normal; or 24 hr stool weight >200 g (physiological definition, less useful clinically)

Classification

- small volume (tablespoons of stool; typical of colonic diseases) versus large volume (>1/2 cup stool; typical of small bowel diseases)
- acute vs. chronic
- watery (bowel disease) vs. steatorrhea
- secretory (diarrhea persists with fasting) vs. osmotic (diarrhea stops with fasting)

Table 8. Classification of Diarrhea

Acute	Chronic	
Infectious	Functional	Neoplastic
• Bacterial	• IBS	• Medullary thyroid carcinoma
• Viral	• Constipation with overflow diarrhea	• Gastrinoma
• Parasitic	Inflammatory	• VIPoma
• Fungal (rare)	• IBD (UC, CD)	• Small bowel lymphoma
Iatrogenic	• Microscopic/collagenous colitis	• Carcinoid tumours
• Drugs	Maldigestion/malabsorption	• Colorectal cancer
• Surgery	• Pancreatic disease (chronic pancreatitis, autoimmune pancreatitis, malignancy)	• Large villous adenoma of rectum
• Radiation	• Celiac disease	Iatrogenic
Osmotic agents	• Short bowel syndrome	• Drugs, alcohol, caffeine
• Lactose	• Small intestinal bacterial overgrowth	• Surgery
• Sugars (sorbitol, mannitol, xylitol etc.)	Metabolic	• Radiation
• Laxative abuse	• Hyperthyroidism	• Laxative abuse
	• Addison's disease	Miscellaneous
	• Uremia	• Chronic mesenteric ischemia
	• Cystic fibrosis	• Incontinence

**Acute Diarrhea****Definition**

- passage of frequent unformed stools for <14 days

Etiology

- most commonly due to infections
- most infections are self-limiting and resolve in 7 days

Risk Factors

- food (seafood, chicken, turkey, eggs, beef)
- medications: antibiotics, laxatives
- others: high risk sexual activity, infectious outbreaks, family history (IBD)

Classification

- broadly divided and classified into inflammatory and non-inflammatory diarrhea
- mechanisms:
 - stimulation of intestinal water secretion and inhibition of water absorption (i.e. secretory problem)
 - in inflammatory diarrhea, organisms and cytotoxins invade mucosa, killing mucosal cells, further perpetuating the diarrhea

Table 9. Classification of Acute Diarrhea

	Inflammatory	Non-inflammatory
Definition	Disruption of intestinal mucosa	No disruption of intestinal mucosa
Site	Small bowel ± colon	Usually small intestine
Sigmoidoscopy	Usually abnormal mucosa seen	Usually normal
Symptoms	Bloody (not always) Small volume, high frequency Often lower abdominal cramping with urgency ± tenesmus May have fever ± shock	Watery, little or no blood Large volume Upper/periumbilical pain/cramp ± shock
Investigations	Fecal WBC and RBC positive	Fecal WBC negative
Etiology	Infectious <ul style="list-style-type: none"> • Bacterial <ul style="list-style-type: none"> <i>Shigella</i> <i>Salmonella typhi</i> <i>Campylobacter</i> <i>Yersinia</i> <i>E. coli</i> (EHEC 0157:H7) <i>C. difficile</i> • Protozoal <ul style="list-style-type: none"> <i>E. histolytica</i> (amebiasis) <i>Strongyloides</i> Drugs <ul style="list-style-type: none"> NSAIDs Inflammatory bowel disease 	Infectious <ul style="list-style-type: none"> • Bacterial <ul style="list-style-type: none"> <i>Salmonella enteritidis</i> <i>S. aureus</i> <i>B. cereus</i> <i>C. perfringens</i> <i>E. coli</i> (ETEC, EPEC) <i>Vibrio cholerae</i> • Protozoal <ul style="list-style-type: none"> <i>Giardia lamblia</i> • Viral <ul style="list-style-type: none"> Rotavirus Norwalk CMV Drugs <ul style="list-style-type: none"> Antacids (Mg: Makes you Go) Antibiotics Laxatives, lactulose Colchicine
Differential Diagnosis	Acute presentation of a chronic diarrheal condition	Chronic diarrheal illness
Significance	Higher yield with stool C&S Can progress to life-threatening megacolon, perforation, hemorrhage	Lower yield with stool C&S Chief life-threatening problem is fluid depletion and electrolyte disturbances

Investigations

- stool cultures/microscopy (C&S/O&P)
 - C&S only tests *Campylobacter*, *Salmonella*, *Shigella*, *E. Coli*
 - ♦ other organisms must be ordered separately
- flexible sigmoidoscopy: useful if inflammatory diarrhea suspected
 - biopsies are the most useful method of distinguishing idiopathic IBD (Crohn's disease and ulcerative colitis) from infectious colitis or acute self-limited colitis
- *C. difficile* toxin: indicated when recent/remote antibiotic use, hospitalization, nursing home or recent chemotherapy

Treatment

- fluid and electrolyte replacement orally in most cases, intravenous if severe, extremes of age and coma
- anti-diarrheals
 - ant motility agents: diphenoxylate, loperamide (Imodium®); contraindicated in mucosal inflammation
 - ♦ side effects: abdominal cramps, toxic megacolon
 - absorbants: kaolin/pectin (Kaopectate®), methylcellulose, activated attapulgite
 - ♦ act by absorbing intestinal toxins/micro-organisms, or by coating intestinal mucosa
 - ♦ much less effective than ant motility agents
 - modifiers of fluid transport: bismuth subsalicylate (Pepto-Bismol®) may be helpful
- antibiotics: rarely indicated
 - risks
 - ♦ prolonged excretion of enteric pathogen (especially *Salmonella*)
 - ♦ drug side effects (including *C. difficile* infection)
 - ♦ development of resistant strains



Useful Questions in Acute Diarrhea

Those Fads Wilt

Travel
Homosexual contacts
Outbreaks
Seafood
Extra-intestinal signs of IBD
Family history
Antibiotics
Diet
Steatorrhea
Weight loss
Immunosuppressed
Laxatives
Tumour history



Infectious Causes of Inflammatory Diarrhea

Think "CaSaDiff Coli-EhShY"

Campylobacter
Salmonella
C. difficile
E. coli (EHEC 0157:H7)
E. histolytica
Shigella
Yersinia



Stool Osmotic Gap

Normally, and in secretory diarrhea, stool osmolality (as measured by freezing point depression; almost always about 290 mOsm/kg) is the same as calculated stool osmolality (2 x stool (Na + K)). In osmotic diarrhea, measured stool osmolality > calculated stool osmolality.



S. typhi has a rose spot rash (transient maculopapular rash on anterior thorax, upper abdomen), and a prodrome of high fever, bradycardia, headache and abdominal pain. Diarrhea is not the initial presentation.

- indications for antimicrobial agents in acute diarrhea:
 - ♦ septicemia
 - ♦ prolonged fever with fecal blood or leukocytes
 - ♦ clearly indicated: *Shigella*, *V. cholerae*, *C. difficile*, Traveller's Diarrhea (Enterotoxigenic *E. coli* (ETEC)), *Giardia*, *Entamoeba histolytica*, *Cyclospora*
 - ♦ situational: *Salmonella*, *Campylobacter*, *Yersinia*, non-enterotoxigenic *E. coli*
 - ♦ *Salmonella*: always treat *Salmonella typhi* (typhoid or enteric fever); treat other *Salmonella* only if there is underlying immunodeficiency, hemolytic anemia, extremes of age, aneurysms, prosthetic valve grafts/joints



Traveller's Diarrhea

- see [Infectious Diseases](#), ID18



Chronic Diarrhea

Definition

- passage of frequent unformed stool for >14 days
- differential is similar to that of acute diarrhea, except that the majority of cases are non-infectious

Etiology/Classification

- see [Classification of Diarrhea](#), G14

Investigations

- guided by history
- stool analysis for: *C. difficile* toxin, C&S, O&P ± fecal fat, WBC
- blood for: CBC, chemistry, CRP, TSH, celiac serology (tTG, protein electrophoresis)
- colonoscopy and ileoscopy with biopsy
- small bowel biopsy
- upper GI endoscopy with duodenal biopsy
- wireless small bowel endoscopy capsule (last resort – very costly)
- trial of lactose free diet
 - may delay diagnosis of IBD and celiac disease



Maldigestion and Malabsorption

Definition

- **maldigestion**: inability to break down large molecules in the lumen of the intestine into their component small molecules
- **malabsorption**: inability to transport molecules across the intestinal mucosa to the circulation
- **malassimilation**: encompasses both maldigestion and malabsorption

Etiology

- **maldigestion**
 - inadequate mixing of food with enzymes (e.g. post-gastrectomy)
 - pancreatic exocrine deficiency
 - primary diseases of the pancreas (e.g. cystic fibrosis, pancreatitis, cancer)
 - bile salt deficiency
 - ♦ terminal ileal disease (impaired recycling), bacterial overgrowth (deconjugation of bile salts), rarely liver disease (cholestatic)
 - specific enzyme deficiencies (e.g. lactase)
- **malabsorption**
 - inadequate absorptive surface
 - immunologic or allergic injury (e.g. celiac disease)
 - ♦ infections/infestations (e.g. Whipple's disease, giardiasis)
 - ♦ infiltration (e.g. lymphoma, amyloidosis)
 - ♦ fibrosis (e.g. systemic sclerosis, radiation enteritis)
 - ♦ bowel resection
 - ♦ extensive Crohn's disease
- drug-induced
 - cholestyramine, ethanol, neomycin, tetracycline and other antibiotics
- endocrine
 - e.g. diabetes (complex pathogenesis)

Clinical Features

- symptoms usually vague unless disease is severe
- weight loss, diarrhea, steatorrhea, weakness, fatigue
- manifestations of malabsorption/deficiency (see Table 10)

Table 10. Absorption of Nutrients and Fat Soluble Vitamins

Deficiency	Absorption	Signs and Symptoms	Investigations
Iron	Duodenum, upper jejunum	Hypochromic, microcytic anemia, glossitis, koilonychia (spoon nails), pica	↓ Hb, ↓ serum Fe, ↓ serum ferritin
Calcium	Duodenum, upper jejunum (binds to Ca binding-protein in cells; levels increased by Vit D)	Metabolic bone disease, may get tetany and paresthesias if serum calcium falls (see Endocrinology , E40)	↓ serum Ca, serum Mg, and ↑ ALP evaluate for ↓ bone mineralization radiographically (DEXA)
Folic acid	Jejunum	Megaloblastic anemia, glossitis, ↓ red cell folate (but may see ↑ folic acid with bacterial overgrowth)	↓ serum folic acid
Vitamin B₁₂	B ₁₂ ingested and bound to R proteins mainly from salivary glands; stomach secretes Intrinsic Factor (IF) in acidic medium; in basic medium, proteases from the pancreas cleave R protein and B ₁₂ -IF complex forms, protecting B ₁₂ from further protease attack; B ₁₂ absorbed in ileum and binds to transcobalamin (TC)	Subacute combined degeneration of the spinal cord, peripheral/optic neuropathy, dementia, megaloblastic anemia, glossitis	Differentiate causes by Schilling test (see Table 11)
Carbohydrate	Complex polysaccharides hydrolyzed to oligosaccharides and disaccharides by salivary and pancreatic enzymes Monosaccharides absorbed in duodenum/jejunum	Generalized malnutrition, weight loss, flatus and diarrhea	Hydrogen breath test Trial of CHO-restricted diet D-xylose test
Protein	Digestion at stomach, brush border, and inside cell Absorption occurs primarily in the jejunum	General malnutrition and weight loss, amenorrhea and ↓ libido if severe	↓ serum albumin (low sensitivity)
Fat	Lipase, colipase, phospholipase A (pancreatic enzymes) and bile salts needed for digestion Products of lipolysis form micelles which solubilize fat and aid in absorption Fatty acids diffuse into cell cytoplasm	Generalized malnutrition, weight loss and diarrhea Foul-smelling feces + gas (steatorrhea)	Small bowel biopsy MRCP, ERCP, pancreatic function tests Quantitative stool fat test (72 hr) (Sudan stain of stool) (C-triolein breath test)
Vitamin A	From plants	Night blindness Dry skin Keratomalacia	
Vitamin D	Skin (via UV light) or diet	Osteomalacia in adults Rickets in children	
Vitamin E	From food	Retinopathy, neurological problems	
Vitamin K	Synthesized by intestinal flora ↑ risk of deficiency after prolonged use of broad spectrum antibiotics and/or starvation	Prolonged INR causes bleeding	

Investigations

- 72 hour stool collection (weight, fat content)
- serum carotene, folate, Ca, Mg, vitamin B₁₂, albumin, ferritin, serum iron solution, INR/PTT
- stool fat globules on fecal smear (rarely used)
- other tests specific for etiology (e.g. CT scan/MRI to visualize pancreas)
- trial of therapy with pancreatic enzymes

Treatment

- dependent on underlying etiology

Table 11. Schilling Test

Part I	<ul style="list-style-type: none"> • 1000 mcg B₁₂ s.c. injection to saturate liver stores • Standard dose radioactively labelled B₁₂ PO • 48hr urine collection; measure amount labelled B₁₂; normal ≥10% of oral dose
Part II	<ul style="list-style-type: none"> • If urine B₁₂ low, repeat part I giving intrinsic factor with oral radiolabelled B₁₂
Interpretation	<ul style="list-style-type: none"> • If part II is normal, diagnosis pernicious anemia • If part II remains low, options are <ol style="list-style-type: none"> 1) Repeat part II, on day 6 and 7 of a 7-day course tetracycline 500 mg PO bid; if Schilling normalizes diagnosis bacterial overgrowth 2) Repeat part II adding pancreatic enzymes; if Schilling normalizes, diagnosis pancreatic insufficiency 3) If test remains low after 1) and 2), consider R protein deficiency, ileal receptor disease, severe extensive ileal Crohn's disease or failure to obtain history of ileal resection



Fat Soluble Vitamins: ADEK



Vitamin K dependent coagulation factors: II, VII, IX, X, protein C, protein S
Think: "1972 Olympics Canada versus the Soviet Union".

**Gluten found in "BROW"**

Barley

Rye

Oats (controversial)

Wheat

Celiac Disease (Gluten Enteropathy/Sprue)

Definition

- abnormal small intestine mucosa due to intestinal reaction to gliadin, a component of gluten

Etiology

- only autoimmune disease in which antigen (alpha-gliadin) is recognized
- associated with other autoimmune diseases, especially thyroid disease
- gluten, a protein in cereal grains, broken down to gliadin, is toxic factor
- HLA-DQ2 (chromosome 6) found in 80-90% of patients compared with 20% in general population; also associated with HLA-DQ8

Epidemiology

- more common in women
- family history: 15% of first-degree relatives
- may present any time from infancy (when cereals introduced) to elderly
- peak presentation in infancy and old age

Clinical Features

- classically: diarrhea, weight loss, anemia, symptoms of vitamin/mineral deficiency, failure to thrive; now more commonly bloating, gas, iron deficiency
- improves with gluten-free diet, deteriorates when gluten reintroduced
- disease is usually most severe in proximal bowel
 - thus iron, calcium and folic acid deficiency more common than vitamin B₁₂ deficiency
- gluten enteropathy may be associated with dermatitis herpetiformis skin eruption, epilepsy, myopathy, depression, paranoia, infertility, bone fractures/metabolic bone disease

Investigations

- small bowel mucosal biopsy (usually duodenum) is usually diagnostic:
 - villous atrophy and crypt hyperplasia
 - increased number of plasma cells and lymphocytes in lamina propria
 - similar pathology in: small bowel overgrowth, Crohn's, lymphoma, Giardia, HIV
- consider CT enterography to visualize small bowel to rule out lymphoma
- evidence of malabsorption (localized or generalized)
 - steatorrhea
 - low levels of ferritin/iron saturation, Ca, Fe, albumin, cholesterol, carotene, B₁₂ absorption
- improvement with a gluten-free diet; should not be started before anti-TTG and biopsy
- serological tests
 - serum anti-TTG antibody, IgA, is 90-98% sensitive, 94-97% specific
 - IgA deficient patients have false-negative anti-TTG
 - ♦ thus measure serum IgA concomitantly (via serum protein electrophoresis)
- fecal fat >7% over 72 hrs

Treatment

- dietary counselling
 - gluten free diet: avoid barley, rye, wheat
 - ♦ oats allowed if not contaminated by other grains
 - rice and corn flour are acceptable
 - iron, folate supplementation (with supplementation of other vitamins as needed)
- if disappointing response to diet, consider:
 - incorrect diagnosis
 - non-adherence to gluten-free diet
 - unsuspected concurrent disease (e.g. microscopic colitis, pancreatic insufficiency)
 - development of intestinal (enteropathy-associated T-cell) lymphoma (abdominal pain, weight loss, palpable mass)
 - development of diffuse intestinal ulceration, characterized by aberrant intraepithelial T-cell population (precursor to lymphoma)

Prognosis

- associated with increased risk of lymphoma, carcinoma (e.g. small bowel and colon)
- risk of malignancy may be lowered by dietary gluten restriction

Gluten Microchallenge with Wheat-based Starch Hydrolysates in Celiac Disease Patients

Aliment Pharmacol Ther 2008; 28:1240-8

Study: Randomized, placebo-controlled, prospective study with 24 week follow-up.

Participants: 90 patients with celiac disease in remission.

Intervention: Patients either received glucose syrups, maltodextrins or placebo.

Primary Outcome: Small bowel mucosal morphology and inflammation, symptoms, celiac serology and malabsorption.

Results: There were significant differences on deleterious effects in small-bowel morphology or inflammation, gastrointestinal symptoms, serology or malabsorption parameters after 24 weeks compared to the placebo group.

Conclusion: Celiac patients can safely continue to consume wheat-based starch hydrolysates, glucose syrups and maltodextrins.

Bacterial Small Bowel Overgrowth

Definition

- syndrome caused by proliferation of bacteria in small bowel to concentrations $>10^4$ bacteria/mL of bowel tissue

Etiology

- anatomic factors
 - jejunal diverticulae
 - surgical blind loop
 - fistulae
 - strictures (Crohn's disease, radiation injury)
 - obstruction
 - surgical resection of the ileocecal valve
- decreased motility
 - scleroderma
 - diabetes
 - hypothyroid
 - intestinal pseudo-obstruction
- achlorhydria (often iatrogenic): lack of gastric acid production
- multifactorial (controversial) in chronic pancreatitis, celiac disease, irritable bowel syndrome
- described in elderly patients without known etiology

Clinical Features

- steatorrhea: bacteria deconjugate bile salts impairing micellar lipid formation
- diarrhea: bowel mucosa damaged by bacterial products, impairing absorption; altered gut motility, free bile acids stimulate colon water secretion
- megaloblastic anemia due to vitamin B₁₂ malabsorption (bacteria take up B₁₂)
- bloating, flatulence
- may be asymptomatic

Investigations

- gold standard: mixed bacterial cultures of $>10^4$ CFU/mL from the jejunum (via aspiration)
- 72-hour fecal fat collection
- bile acid breath tests
- positive three stage Schilling test if done before and after treatment can be diagnostic (see Table 11)
- low serum B₁₂, high serum folate (folate synthesized by GI bacteria)
- CT enterography to look for underlying cause
- consider small bowel biopsy to rule out primary mucosal disease as cause of malabsorption

Treatment

- treat underlying etiology if possible (e.g. prokinetic agents for small bowel motility disorder, surgery or balloon dilatation for strictures)
- correct nutritional deficiencies, especially deficiencies of vitamins A, D, E, K, B₁₂
- often need to restrict lactose since underlying disease often causes lactose intolerance
- eradicate bacteria: 10-14 day trial of antibiotics (best if based on culture results)
 - e.g. amoxicillin + clavulanic acid, norfloxacin, neomycin
- patients may need to be treated with intermittent or continuous antibiotics indefinitely
 - rotate antibiotics to decrease development of resistance
- discontinue acid-reducing agents if possible

Inflammatory Bowel Disease (IBD)



Definition

- Crohn's disease (CD), ulcerative colitis (UC), indeterminate colitis, microscopic and collagenous colitis

Pathophysiology

- poorly understood
- sustained response of the immune system, perhaps to enteric flora in a genetically predisposed individual
- current hypothesis: lack of appropriate down-regulation of immune responsiveness

Genetics

- increased risk of both ulcerative colitis and Crohn's disease in relatives of patients with either disease, especially siblings, early onset disease
 - familial risk greater if proband has Crohn's than ulcerative colitis

- likely polygenomic pattern: 9 gene loci described to be associated
- CARD15 gene mutation associated with Crohn's (relative risk in heterozygote is 3, in homozygote is 40), especially Ashkenazi Jews, early onset disease, ileal involvement, fistulizing and stenotic disease (NOD2)
 - CARD15 gene product modulates NFκB, which is required for the innate immune response to microbial pathogens, best expressed in monocytes-macrophages

Clinical Features

Table 12. Clinical Differentiation of Ulcerative Colitis from Crohn's Colitis Disease

	Crohn's Disease	Ulcerative Colitis
Location	Any part of GI tract <ul style="list-style-type: none"> • Small bowel + colon: 50% • Small bowel only: 30% • Colon only: 20% 	Isolated to large bowel Always involves rectum, may progress proximally
Rectal Bleeding	Uncommon	Very common (90%)
Diarrhea	Less prevalent	Frequent small stools
Abdominal Pain	Post-prandial/colicky	Pre-defecatory urgency
Fever	Common	Uncommon
Palpable Mass	Frequent (25%), RLQ	Rare (if present, cecum full of stool)
Recurrent After Surgery	Common	None post-colectomy
Endoscopic Features	Discrete aphthous ulcers, patchy lesions, pseudopolyps	Continuous diffuse inflammation, erythema, friability, loss of normal vascular pattern, pseudopolyps
Histologic Features	Transmural distribution with skip lesions Focal inflammation ± noncaseating granulomas, deep fissuring + aphthous ulcerations, strictures Glands intact	Mucosal distribution, continuous disease (no skip lesions) Granulomas absent Gland destruction, crypt abscess
Radiologic Features	Cobblestone mucosa Frequent strictures and fistulae XR: Bowel wall thickening "string sign"	Lack of haustra Strictures rare and suggests complicating cancer
Complications	Strictures, fistulae, perianal disease	Toxic megacolon
Colon Cancer Risk	More than general population	More than general population



Crohn's Disease

Definition

- chronic inflammatory disorder potentially affecting the entire gut "from gum to bum"

Epidemiology

- incidence 1-6/100,000; prevalence 10-100/100,000
- bimodal: onset before 30 years, second smaller peak age 60
- incidence of Crohn's increasing (relative to UC) especially in young females
- more common in Caucasians, Ashkenazi Jews
 - risk in Asians increases with move to Western countries
- M=F; smoking incidence in Crohn's patients is higher than general population

Clinical Features

- natural history unpredictable
- most often presents as recurrent episodes of abdominal cramps, diarrhea and weight loss
- most common location: ileum + ascending colon
- ileitis may present with post-prandial pain, vomiting, RLQ mass; mimics acute appendicitis
- fistulae, fissures, abscesses are common
- extra-intestinal manifestations (see Table 13) are more common with colonic involvement
- linear ulcers leading to mucosal islands and "cobblestone" appearance
- deep fissures with risk of perforation into contiguous viscera (leads to fistulae and abscesses)
- enteric fistulae may communicate with skin, bladder, vagina and other parts of bowel
- granulomas are found in 50% of surgical specimens, 15% of mucosal biopsies

Investigations

- colonoscopy with biopsy to visualize (less often gastroscopy)
- CT enterography to visualize small bowel
- CRP elevated in most new cases, useful to monitor treatment response
- bacterial cultures, O&P, *C. difficile* toxin to exclude other causes of inflammatory diarrhea

Management (see Figure 7)

- smoking cessation
- medical management (most uncomplicated cases can be managed medically)
- diet
 - fluids only diet at start of acute exacerbation
 - enteral diets may aid in remission
 - apart from enteral diet, no evidence for any diet changing the natural history of Crohn's disease, but may affect symptoms
 - those with extensive small bowel involvement or extensive resection require electrolyte, mineral and vitamin supplements (vit D, Ca, Mg, zinc, Fe, B₁₂)
- 5-ASA
 - efficacy controversial: most evidence for mild colonic disease
 - sulfasalazine (Salazopyrin®): 5-ASA bound to sulfapyridine
 - ♦ hydrolysis by intestinal bacteria releases 5-ASA (active component)
 - ♦ dose-dependent efficacy
 - mesalamine (Pentasa®): coated 5-ASA releases 5-ASA in the ileum and colon
- antibiotics
 - e.g. metronidazole (20 mg/kg/d, bid or tid dosing)
 - best described for perianal Crohn's, although characteristically relapse when discontinued
 - side effects are common and reversible for metronidazole
 - ♦ 50% have peripheral neuropathy after 6 months of treatment, may not be reversible
 - ciprofloxacin also useful
- corticosteroids
 - prednisone: starting dose usually 40 mg OD for acute exacerbations; intravenous methylprednisolone if severe, then tapered
 - no proven role for steroids in maintaining remissions; masks intra-abdominal sepsis
 - complications of steroid therapy are dose and duration dependent
 - ♦ note: budesonide has fewer side effects than prednisone; start at 9 mg daily
- immunosuppressives
 - 6-mercaptopurine (6-MP), azathioprine (Imuran®); methotrexate used less often
 - more often used to maintain remission than to treat active inflammation
 - most commonly used as steroid-sparing agents
 - ♦ i.e. to lower risk of relapse as corticosteroids are withdrawn
 - may require >3 months to have beneficial effect; usually continued for several years
 - may help to heal fistulae, decrease disease activity
 - side effects: vomiting, pancreatitis, bone marrow suppression, increased risk of malignancy
- antidiarrheal agents
 - loperamide (Imodium®) > diphenoxylate (Lomotil®) > codeine (cheap but addictive)
 - all work by decreasing small bowel motility
 - caution if colitis is severe (risk of precipitating toxic megacolon)
 - avoid if significant mucosal inflammation
- cholestyramine
 - a bile-salt binding resin
 - for watery diarrhea with <100 cm of terminal ileum diseased or resected
 - however, non-specific anti-diarrheals are more convenient and often more potent
- biologicals
 - infliximab IV (Remicade®) or adalimumab SC (Humira®): antibody to TNF- α
 - proven effective for treatment of fistulae and patients with medically refractory CD
 - first-line immunosuppressive therapy with infliximab + immunosuppressives more effective than using either alone
 - anti-TNF therapy often effective within days, generally well-tolerated
 - side effect: reported cases of reactivated TB, PCP, other infections
- surgical treatment (see **General Surgery**, GS29)
 - surgery generally reserved for complications such as fistulae, obstruction, abscess, perforation, bleeding and for medically refractory disease
 - ♦ if <50% or <200 cm of functional small intestine, risk of short bowel syndrome
 - at least 50% clinical recurrence within 5 years; 85% within 15 years; endoscopic recurrence rate even higher
 - 40% likelihood of second bowel resection, 30% likelihood of third bowel resection
 - complications of ileal resection:
 - ♦ <100 cm resected \rightarrow watery diarrhea (impaired bile salt absorption)
 - treatment: cholestyramine or anti-diarrheals e.g. loperamide
 - ♦ >100 cm resected \rightarrow steatorrhea (reduced mucosal surface area, bile salt deficiency)
 - treatment: fat restriction, medium chain triglycerides prn

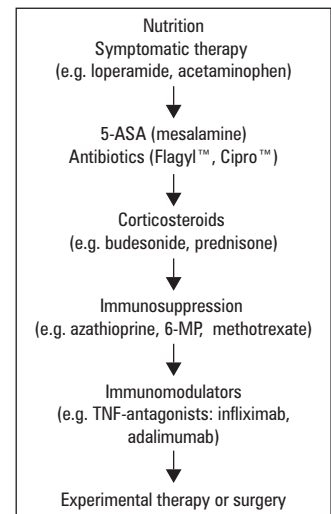


Figure 7. Traditional Graded Approach to Induction Therapy in Crohn's

Medical Management of Crohn's

	Induced Remission	Maintenance
5-ASA	+	?
Steroids	+	
Immunosuppressive	+	+
Antibiotics	+	
MTX	+	+
Infliximab	+	+



Characteristically more than 1 year between onset of symptoms and diagnosis of Crohn's disease.

Biological Therapies for Inflammatory Bowel Diseases

Gastroenterol 2009; 136:1182-97

Although the etiology of inflammatory bowel diseases (IBD) is unknown, biological therapies (BT) that target key molecules in innate and adaptive immune pathways have been designed.

Anti-TNF: (infliximab, adalimumab, certolizumab) It improves treatment of CD, less for UC. It increases mucosal healing, decreases need for hospitalizations and surgeries, and can induce steroid-free remission. At least 10% of patients annually develop intolerance and/or a loss of response.

Selective Anti-Adhesion Molecules: (natalizumab) It increases response and remission rates, circulating leukocytes and steroid-sparing capacity in CD. Progressive multifocal leukoencephalopathy is a rare adverse event.

Promising New BT: Anti-Interleukin-12/ Interleukin-23 p40 target factors more often associated with CD, while anti-IFN-antibodies may treat CD and UC.

BT Without Established Efficacy: Recombinant human cytokines, blockade of T-cell activation (dacizumab and basiliximab) and stimulators of the innate immune system.

Conclusion: Anti-TNF is an effective treatment for IBD. There is a need to develop an effective treatment for patients who do not respond to a first biological drug. BT's have a safety risk, so their place in treatment algorithms must be defined carefully.

Prognosis

- highly variable course
- 10% chronic, relapsing
- 10% disabled by the disease eventually
- increased mortality, especially with more proximal disease, greatest in the first 4-5 years
- intestinal obstruction due to edema, fibrosis
- fistula formation
- intestinal perforation characteristically contained (free perforation uncommon)
- malignancy: increased risk especially with colonic involvement, but less risk compared to ulcerative colitis
- surveillance colonoscopy same as ulcerative colitis (see below) if more than 1/3 of colon involved

**Ulcerative Colitis (UC)****Definition**

- inflammatory disease affecting colonic mucosa anywhere from rectum to cecum, but rectum always involved

Epidemiology

- incidence 2-10/100,000; prevalence 35-100/100,000 (more common than Crohn's)
- 2/3 onset by age 30 (with second peak after 50); M=F
- small hereditary contribution (15% of cases have 1st degree relative with disease)
- risk is less in smokers
- inflammation limited to rectum or left colon more common than pancolitis

Pathology

- disease can involve any portion of lower bowel from rectum only (proctitis) to entire colon (pancolitis)
- rectum always involved
- inflammation diffuse, continuous and confined to mucosa

Clinical Features

- chronic disease most frequently characterized by diarrhea and rectal bleeding
 - can also have abdominal cramps/pain, especially with defecation
- severity of colonic inflammation correlates with symptoms (stool volume, amount of blood in stool)
- tenesmus, urgency, incontinence
- systemic symptoms: fever, anorexia, weight loss, fatigue in severe cases
- extra-intestinal manifestations (see Table 13)
- characteristic exacerbations and remissions; 5% of cases are fulminant



In UC's initial presentation, non-bloody diarrhea is frequently seen; eventually progresses to bloody diarrhea.

Investigations

- sigmoidoscopy with mucosal biopsy (to exclude self-limited colitis) without bowel prep often sufficient for diagnosis
- colonoscopy helpful to determine extent of disease; contraindicated in severe exacerbation
- CT colonography (formerly barium enema) if colonoscopy cannot be done; contraindicated in severe disease
- stool culture, microscopy, *C. difficile* toxin assay necessary to exclude infection
- no single confirmatory test

Management

- mainstays of treatment: 5-ASA derivatives and corticosteroids, with azathioprine used in steroid-dependent or resistant cases
- diet of little value in decreasing inflammation but may alleviate symptoms
- antidiarrheal medications generally not indicated in UC
- 5-ASA
 - topical (suppository or enema): very effective for distal disease (distal to splenic flexure), preferable to corticosteroids
 - oral: effective for mild to moderate, but not severe colitis
 - e.g. sulfasalazine 3-4 g/d, mesalamine 4 g/d
 - useful only for mild to moderate disease, not for severe disease
 - more commonly used in maintaining remission (decreases yearly relapse rate from 60% to 15%)
 - may decrease rate of colorectal cancer

- corticosteroids
 - to remit acute disease, especially if severe or first attack; may need maximum dose IV steroids initially (e.g. methylprednisolone 30 mg IV q12h)
 - limited role as maintenance therapy
 - use suppositories for proctitis, enemas for proctosigmoiditis
 - topical steroids (e.g. hydrocortisone foam, budesonide enemas) for inflammation distal to splenic flexure
- immunosuppressants (steroid-sparing)
 - if severe UC is refractory to steroid therapy, consider adding IV cyclosporine or IV infliximab – rapidly effective but helpful only in a minority of patients
 - azathioprine: too slow to rapidly resolve acute relapse
 - ◆ most commonly used to induce and maintain remission as corticosteroids withdrawn
 - infliximab entering routine clinical use
- surgical treatment
 - early in severe especially fulminant cases and toxic megacolon – consider operation if no response after 5 days of medical therapy
 - aim for cure with colectomy
 - indications: failure of adequate medical therapy, toxic megacolon, bleeding, pre-cancerous changes picked up by screening endoscopic biopsies (dysplasia)

Medical Management of Ulcerative Colitis

	Induced Remission	Maintenance
5-ASA	+	+
Steroids	+	
Immunosuppressive	+/-	+

Complications

- similar to CD, except:
 - more liver problems (especially primary sclerosing cholangitis [PSC] in men)
 - greater risk of colorectal cancer
 - ◆ risk increases with duration and extent of disease (5% at 10 years, 15% at 20 years for pancolitis; overall RR is 8%)
 - ◆ risk also increases with presence of sclerosing cholangitis, family history of colorectal cancer
 - ◆ thus, regular colonoscopy and biopsy in pancolitis of ≥ 8 years is indicated
 - toxic megacolon (transverse colon diameter >6 cm on abdominal x-ray) with immediate danger of perforation (see General Surgery, GS29)

Prognosis

- chronic relapsing pattern in most patients
- 10-15% chronic continuous pattern
- >1 attack in almost all patients
- more colonic involvement in the 1st year correlates with increased severity of attacks and increased colectomy rate
 - colectomy rate = 1% for all patients after the 1st year; 20-25% eventually undergo colectomy
- normal life expectancy
- if proctitis only, usually benign course


When Considering Complications of IBD, Think: ULCERATIVE COLITIS

Urinary Calculi
 Liver problems
 Cholelithiasis
 Epithelial problems
 Retardation of growth/sexual maturation
 Arthralgias
 Thrombophlebitis
 Iatrogenic complications
 Vitamin deficiencies
 Eyes
 Colorectal cancer
 Obstruction
 Leakage (perforation)
 Iron deficiency
 Toxic megacolon
 Inanition (wasting)
 Strictures, fistulae

Table 13. Extraintestinal Manifestations of IBD

System	Crohn's Disease	Ulcerative Colitis
Dermatologic		
Erythema Nodosum	15%	10%
Pyoderma Gangrenosum	10%	Less common
Perianal skin tags	75-80%	Rare
Oral mucosal lesions	Common	Rare
Psoriasis	Statistically associated in 5-10% of those with IBD but not an EIM	
Rheumatologic		
Peripheral arthritis	15-20% of those with IBD (CD>UC)	
Ankylosing Spondylitis	10% of those with IBD (CD>UC)	
Sacroiliitis	Occurs equally in CD and UC	
Ocular (~10% of IBD)		
Uveitis (vision threatening)		
Episcleritis (benign)	3-4% of IBD patients (CD>UC)	
Hepatobiliary		
Cholelithiasis	15-35% of patients with ileal Crohn's	
Primary sclerosing cholangitis (PSC)	1-5% of IBD cases involving colon	
Fatty liver		
Urologic		
Calculi	Most common in CD, especially following ileal resection	
Ureteral obstruction		
Fistulas	Characteristic of Crohn's	
Others		
Thromboembolism		
Vasculitis		
Osteoporosis		
Vitamin deficiencies (B ₁₂ , Vit ADEK)		
Cardiopulmonary disorders		
Pancreatitis (rare)		



Irritable Bowel Syndrome (IBS)

Definition

- a form of functional, but specific bowel disease, not just a label for all GI symptoms that are unexplained after investigation

Epidemiology

- 20% of North Americans
- onset of symptoms usually in young adulthood
- F>M

Pathophysiology

- normal perception of abnormal gut motility vs. abnormal perception of normal gut motility
- abnormal motility: multiple abnormalities described, may be causative
- psychological: stress may increase IBS symptoms but does not cause IBS

Diagnosis

Table 14. Rome III Criteria for Diagnosing Irritable Bowel Syndrome

IBS Rome III Criteria	
<ul style="list-style-type: none"> • ≥12 weeks in the past 12 months of abdominal discomfort or pain that has 2 out of 3 features: <ul style="list-style-type: none"> • Relieved with defecation • Associated with a change in frequency of stool • Associated with a change in consistency of stool • The following are supportive, but not essential to the diagnosis: <ul style="list-style-type: none"> • Abnormal stool frequency (>3/day or <3/week) • Abnormal stool form (lumpy/hard/loose/watery) >1/4 of defecations • Abnormal stool passage (straining, urgency, feeling of incomplete evacuation) >1/4 of defecations • Passage of mucus >1/4 of defecations 	
Diagnosis of IBS less likely in presence of "Alarm" Features	
<ul style="list-style-type: none"> • Weight loss • Fever • Nocturnal defecation 	<ul style="list-style-type: none"> • Anemia • Blood or pus in stool • Abnormal gross findings on flexible sigmoidoscopy
Normal Physical Exam	

Investigations

- not required if history consistent with Rome III criteria or younger patient, no alarm symptoms
- aim is to rule out:
 - enteric infections e.g. *Giardia*
 - lactose intolerance/other disaccharidase deficiency
 - Crohn's disease
 - celiac sprue
 - drug-induced diarrhea
 - diet-induced (excess tea, coffee, colas)
- CBC, TSH, albumin, CRP, tTG serology with protein electrophoresis
- stool for C&S, O&P, fat excretion if diarrhea present
- consider sigmoidoscopy

Management

- reassurance, explanation, support, aim for realistic goals
- relaxation therapy, biofeedback, hypnosis, stress reduction
- bran or psyllium for constipation, loperamide for diarrhea
- no therapeutic agent consistently effective
 - tricyclic antidepressants may provide visceral analgesia
- symptom-guided treatment
 - pain predominant
 - ♦ antispasmodic medication before meals (e.g. hyosine, pinaverium, trimebutine)
 - ♦ increased fibre diet
 - ♦ tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI)
 - ♦ visceral antinociceptive agent
 - diarrhea predominant
 - ♦ increase fibre in diet to increase stool consistency
 - ♦ loperamide 2-4 mg tid/qid
 - ♦ diphenoxylate (Lomotil®)
 - ♦ cholestyramine 4 g qid
 - constipation predominant
 - ♦ exercise and adequate fluid intake
 - ♦ increase fibre in diet
 - ♦ osmotic or other laxatives

Prognosis

- 80% improve over time
- most have intermittent episodes
- normal life expectancy

Constipation

**Definition**

- passage of infrequent or hard stools with straining (stool water <50 mL/day); bowel frequency <3 times/week

Epidemiology

- increasing prevalence with age, F>M
- rare in Africa and India where stool weight is 3-4x greater than in Western countries

Etiology

- most common: colon dysmotility
- organic causes
 - medication side effects (narcotics, antidepressants), most common
 - intestinal obstruction, left sided colon cancer (consider in older patients), fecal impaction
 - metabolic
 - ♦ diabetes mellitus (DM)
 - ♦ hypothyroidism
 - ♦ hypercalcemia, hypokalemia, uremia
 - neurological
 - ♦ intestinal pseudo-obstruction
 - ♦ Parkinson's disease
 - ♦ multiple sclerosis (MS)
 - collagen vascular disease (e.g. scleroderma)
 - painful anal conditions (e.g. fissures)

**Causes of Constipation**

DOPED
 Drugs
 Obstruction
 Pain
 Endocrine dysfunction
 Depression

Clinical Presentation

- overlaps with irritable bowel syndrome
- abdominal pain relieved by defecation, hard stools, straining and pain with defecation, flatulence, overflow diarrhea, sense of incomplete evacuation, abdominal distention, <3 BM/week

Investigations

- consider colon visualization (colonoscopy, CT colonography), although chronic constipation by itself is rarely due to colonic mucosal disease
- classification based on colon transit time, can be quantitated by swallowing radio-opaque markers to measure colonic transit time (normal: 70 hours)
 - (1) normal = misperception of normal defecation, probably form of irritable bowel syndrome
 - (2) prolonged throughout = "colonic inertia" (infrequent bowel movements with gas/bloating, tends to occur in youth)
 - (3) outlet obstruction = inability to coordinate pelvic floor muscles to empty rectum, straining, stool in rectum on digital exam, tends to occur in old age
- combination of (2) and (3) common

Treatment (in order of increasing potency)

- dietary fibre
 - useful if mild or moderate constipation, but not if severe
 - aim for 30 g daily, increase dose slowly
- surface-acting (soften and lubricate)
 - docusate salts, mineral oils
- osmotic agents (effective in 2-3 days)
 - lactulose, sorbitol, magnesium citrate, magnesium sulfate, magnesium hydroxide, lactitol, Milk of Magnesia, polyethylene glycol 3350
- cathartics (effective in 24 hrs)
 - castor oil, senna (avoid prolonged use to prevent melanosis coli)
- enemas and suppositories (e.g. saline enema, phosphate enema, glycerin suppository)



Upper Gastrointestinal Bleeding

Definition

- bleeding proximal to the ligament of Treitz (75% of GI bleeds)
 - ligament of Treitz: suspensory ligament where fourth portion of the duodenum transitions to jejunum

Clinical Features

- in order of decreasing severity of the bleed: hematochezia > hematemesis > melena > occult blood in stool

Etiology

- above the GE junction
 - epistaxis
 - esophageal varices (10-30%)
 - esophagitis
 - esophageal cancer
 - Mallory-Weiss tear (10%)
- stomach
 - gastric ulcer (20%) (see *Peptic Ulcer Disease*, G11)
 - gastritis (e.g. from alcohol or post-surgery) (20%)
 - gastric cancer
- duodenum
 - ulcer in bulb (25%)
 - aortoenteric fistula: usually only if previous aortic graft (see sidebar)
- coagulopathy (drugs, renal disease, liver disease)
- vascular malformation (Dieulafoy's lesion, AVM)

Management (initial)

- stabilize patient (2 large bore IVs, IV fluids, monitor)
- send blood for CBC, cross and type, platelets, PT, PTT, electrolytes, BUN, Cr, LFTs
- keep NPO
- consider NG tube to determine upper vs. lower GI bleeding in some cases
- endoscopy (OGD): establish bleeding site + treat lesion
 - if bleeding peptic ulcer: most commonly used method of controlling bleeding is injection of epinephrine around bleeding point + thermal hemostasis (bipolar electrocoagulation or heater probe) – less often thermal used alone, but injection alone not recommended
 - endoclips



Aortoenteric Fistula is a rare and lethal cause of GI bleed, most common in patients with a history of aortic graft surgery. Therefore, perform emergency endoscopy if suspected, emergency surgery if diagnosed.

Note: The window of opportunity is narrow. Suspect if history of aortic graft, abdominal pain associated with bleeding.



Always ask about NSAID/aspirin or anticoagulant therapy in GI bleed.

Forrest Classification of Peptic Ulcers

Forrest Class	Type of lesion	Risk of Rebleed (%)
I	Arterial Bleeding (oozing/spurting)	55-100
Ila	Visible Vessel	43
Ilb	Sentinel Clot	22
Ilc	Hematin Covered Flat Spot	10
III	No Stigmata of Hemorrhage	5

Reference: Forrest JA, Finlayson ND, Shearman DJ. Endoscopy in Gastrointestinal Bleeding. *Lancet* 1974; (17):394-397.

- IV PPI: decrease risk of rebleed if endoscopic predictors of rebleeding seen (see below)
 - given to stabilize clot, not to accelerate ulcer healing
 - if given before endoscopy, decreases need for endoscopic therapeutic intervention
- for variceal bleeds, octreotide 50 µg loading dose followed by constant drip of 50 µg/hr
- consider IV erythromycin (or metoclopramide) prior to gastroscopy to remove clots from stomach

Prognosis

- 80% stop spontaneously
- peptic ulcer bleeding: low mortality (2%) unless rebleeding occurs (25% of patients, 10% mortality)
- endoscopic predictors of rebleeding: spurt or ooze, visible vessel, fibrin clot
- can send home if clinically stable, bleed is minor, no comorbidities, endoscopy shows clean ulcer with no predictors of rebleeding
- H₂-antagonists have little impact on rebleeding rates and need for surgery
- esophageal varices have a high rebleeding rate (55%) and mortality (29%)

Bleeding Peptic Ulcer

Clinical Features

- see *Peptic Ulcer Disease*, G11

Management

- OGD to explore upper GI tract (see Figure 8)
- establish risk of rebleeding/continuous bleed
 - risk factors: increased age (>60), bleeding diathesis, previous history of PUD, comorbid disease, hemodynamically unstable
 - ♦ if high risk, consider ICU admission

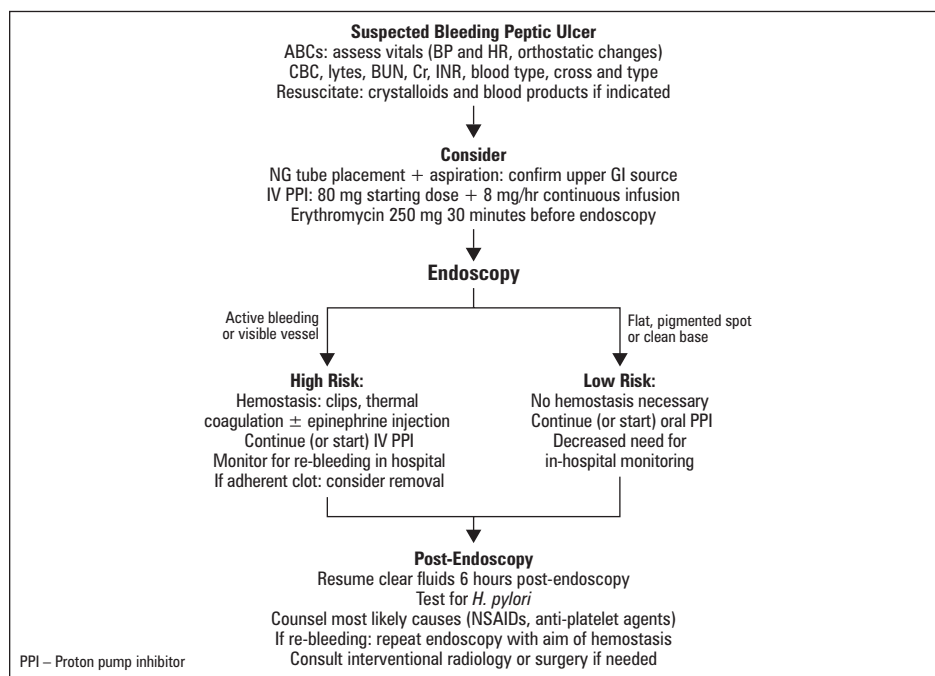


Figure 8. Approach to Management of Suspected Bleeding Peptic Ulcer

Adapted from Gralnek I, Barkun A, Bardou M. Management of acute bleeding from a peptic ulcer. *NEJM* 2008; 359:928-937.

Esophageal Varices

Etiology

- almost always due to portal hypertension
- often accompanied by varices in stomach

Clinical Features

- characteristically massive upper GI bleeding

Investigations

- endoscopy



Bleeding Peptic Ulcers: Risk Factors for Mortality

Co-existent illness
Hemodynamic instability
Age >60 years
Transfusion required

Proton Pump Inhibitor Treatment for Acute Peptic Ulcer Bleeding

Cochrane Database Syst Rev 2006; (1):CD002094

Purpose: To review the efficacy of proton pump inhibitors (PPIs) in acute bleeding from peptic ulcers (PU).

Study Selection: RCTs of PPI treatment compared with placebo or H₂-receptor antagonist (H₂RA) in acute bleeding from PU.

Results: 24 trials (n=4373) were reviewed. There was no significant difference in all-cause mortality rates between PPI and control treatment. PPIs significantly reduced rebleeding compared to control (10.6% PPI versus 17.3% control; OR 0.49), as well as the need for surgery (6.1% PPI versus 9.3% control; OR 0.61).

Conclusion: PPIs should be administered to patients with endoscopically-documented PU bleeding from "high risk" ulcers (ie at high risk of rebleeding: active bleeding, visible vessel, clot) at endoscopy despite the lack of evidence of an overall effect mortality.

Intragastric pH with Oral vs. Intravenous Bolus plus Infusion Proton-pump Inhibitor Therapy in Patients with Bleeding Ulcers

Gastroenterol 2008; 134:1836-41

Study: Randomized control trial.

Participants: Patients presenting with overt bleeding from an ulcer.

Intervention: Patients received either IV lansoprazole (90 mg bolus followed by 9 mg/h infusion; n=32) or oral lansoprazole (120 mg bolus followed by 30 mg every 3 hours; n=34).

Primary Outcome: 24 hour pH

Results: Intragastric pH was > 6 for > 60% of the study period in 22 (68.8%) patients receiving IV and 22 (64.7%) patients receiving oral PPI. At 1 hour, mean pHs for IV and oral were 5.3 and 3.3, respectively (difference 2.0; P=0.001). After 1.5 hours, there were no differences in mean pH between the groups. Mean pH rose above 6 after 2-3 hours of IV PPI and 3-4 hours of oral PPI.

Conclusion: Frequent oral PPI may be able to replace the currently recommended IV bolus plus infusion PPI therapy in patients with bleeding ulcers. However, IV PPI has a more rapid increase in pH, reaching mean pH of 6 approximately 1 hour sooner than oral PPI.



If varices isolated to stomach, think of splenic vein thrombosis.

Management

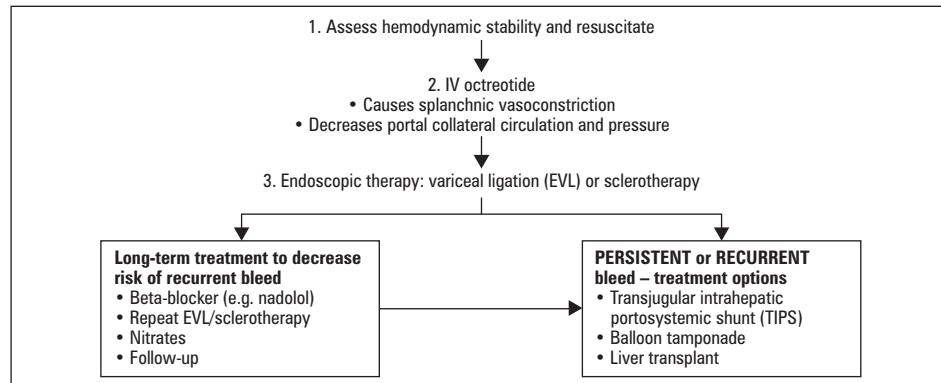


Figure 9. Management of Bleeding Esophageal Varices

Mallory-Weiss Tear

Definition

- longitudinal laceration in gastric mucosa on lesser curvature near GE junction (20% straddle junction, 5% in distal esophagus)

Etiology

- due to rapid increases in gastric pressure (e.g. retching/vomiting against a closed glottis)
- most patients abuse alcohol
- hiatus hernia usually present

Clinical Features

- hematemesis ± melena, classically following an episode of retching
- can lead to fatal hematemesis

Management

- 90% stop spontaneously
- if persistent: endoscopy with injection ± clips or surgical repair



Lower Gastrointestinal Bleeding

Definition

- bleed distal to ligament of Treitz

Etiology

- rule out upper GI source
- diverticular (60% from right colon)
- vascular
 - angiodysplasia
 - anorectal (hemorrhoids, fissures)
- neoplasm
 - cancer
 - polyps
- inflammation
 - colitis (ulcerative, infectious, radiation, ischemic)
- post-polypectomy

Clinical Features

- hematochezia (see Figure 10)
- anemia
- occult blood in stool
- rarely melena



When suspecting lower GI bleed, first and foremost exclude upper GI bleeding before localizing the site of the lower GI bleed.



Lower GI Bleed

CHAND

Colitis [radiation, infectious, ischemic, IBD (UC > CD)]
Hemorrhoids/fissure
Angiodysplasia
Neoplastic
Diverticular disease

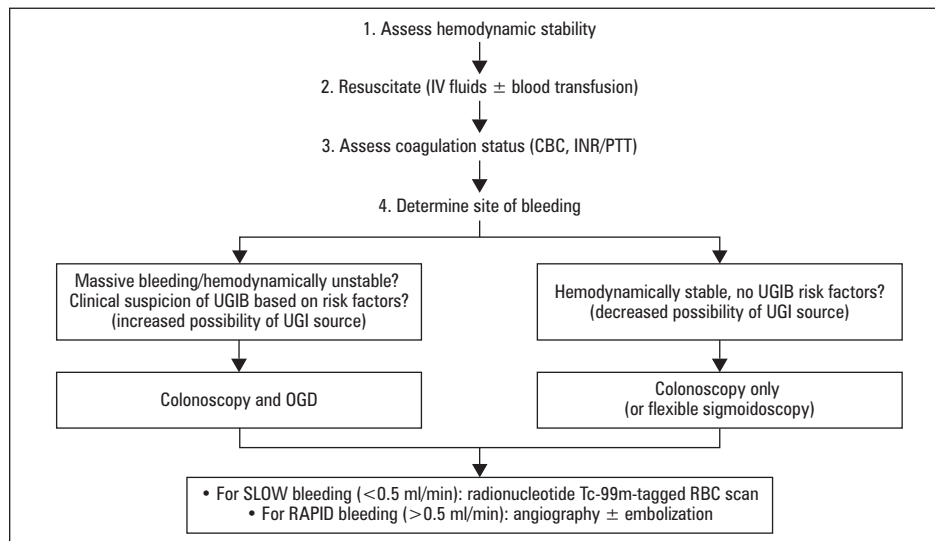


Figure 10. Approach to Hematochezia

Colorectal Cancer

- see General Surgery, GS32

Etiology/Epidemiology

- environmental influences: high dietary fat, low dietary fibre
- genetic influences:
 - all colorectal cancers considered to have genetic component, to varying degrees
 - familial syndromes (see *Familial Colon Cancer Syndromes*, G30)
 - multiple “step-wise” somatic mutations, contributed by environment, have been implicated
 - genetic changes implicated:
 - ♦ activation of proto-oncogenes (K-ras)
 - ♦ loss of tumour-suppressor gene activity (APC, DCC)
 - ♦ abnormalities in DNA repair genes (hMSH2, hMLH1), especially HNPCC syndromes

Pathophysiology

- normal colon → hyperproliferative epithelium → adenoma → carcinoma

Risk Factors

- 75% of new cases are in people with no known risk factors
- age
 - 90% of cancers are in people >50 years old
 - at age 50, the risk of developing colorectal cancer by age 80 is 5%
- adenomatous polyps
- family history
 - sporadic cancer
 - ♦ risk increases 1.8x for those with one affected relative, 2-6x with two affected relatives
 - ♦ risk is greater if relative has cancer diagnosed <45 years old
 - familial adenomatous polyposis and Gardner's syndrome
 - hereditary nonpolyposis colorectal cancer (Lynch syndrome or HNPCC)
- IBD
 - UC – after 10 years, cancer risk increased approximately by 1% for each additional year
 - Crohn's disease – unclear, likely similar to UC if more than 1/3 of colon inflamed

Prevention

- increase fibre in diet, decrease animal fat and red meat, decrease smoking and EtOH, increase exercise and decrease BMI
- aspirin
- secondary prevention with screening (see sidebar)

Prognosis

- stage 1 (limited to wall of bowel): 95%
- stage 2 (through wall of bowel): 80%
- stage 3 (into lymph nodes): 50%

Treatment (see General Surgery)



Some colon cancers may bleed intermittently or not at all. No bleeding does not rule out cancer.



Melena more often seen with right-sided tumours.
Hematochezia more often seen with left-sided tumours.

Colorectal Cancer Screening
Canadian Association of Gastroenterology, *Can J Gastroenterol* 2004; 18(2)

People at average risk:

- >50, no family history should undergo one of:
 - FOBT q 2 years
 - Flexible sigmoidoscopy q 5 years
 - Combined FOBT and flex sig q 5 years
 - Double contrast barium enema q 5 years (more recently CT colonography replaces barium enema)
 - Colonoscopy q 10 years

People at above-average risk:

- HNPCC – Genetic testing + colonoscopy q 2 years beginning at age 20
- FAP – Genetic testing + sigmoidoscopy annually beginning at age 10-12
- Fam Hx of cancer (One or more first degree relatives with CRC i.e. parent, sibling or child) or polyps but does not fit criteria for HNPCC/FAP – colonoscopy q 5 years beginning at age 40 or 10 years earlier than the youngest diagnosed polyp/cancer case in the family.



Colorectal Polyps

Definition

- small mucosal outgrowth into the lumen of the colon or rectum
- sessile (flat) or pedunculated (on a stalk)

Epidemiology

- 30% of population (with no family history or polyps or colorectal cancer) have polyps by age 50, 40% by age 60, 50% by age 70

Clinical Features

- 50% in the rectosigmoid region, 50% are multiple
- usually asymptomatic, but may have rectal bleeding, change in bowel habits (less common)
- usually detected during routine endoscopy or family screening

Pathology

- hyperplastic: most common, no malignant potential, except sessile serrated type
- inflammatory (or pseudopolyps): associated with CD and UC, no malignant potential
- hamartomas: juvenile polyps, Peutz-Jegher syndrome (characteristically small bowel)
 - malignant risk due to associated adenomas (large bowel)
 - low malignant potential → most spontaneously regress or auto-amputate
- adenomas: premalignant, carcinoma in situ may occur
 - some may contain invasive carcinoma ("malignant polyp", 2.6-9.4%): invasion into muscularis
 - tubular, tubulovillous, villous (see Table 15)



Table 15. Characteristics of Tubular vs. Villous Polyps

	Tubular	Villous
Incidence	Common (60% to 80%)	Less common (10%)
Size	Small (<2 cm)	Large (usually >1 cm)
Attachment	Pedunculated/sessile	Sessile
Malignant Potential	Lower	Higher
Distribution	Even	Left-sided predominance

Investigations

- flexible sigmoidoscopy can reach 60% of polyps in men and 35% of polyps in women; if polyps detected, proceed to colonoscopy for examination of entire bowel and biopsy
- colonoscopy remains the gold standard

Treatment

- endoscopic polypectomy; surgical segmental resection if unsuccessful/impossible
- follow-up for adenomas: repeat colonoscopy in 5 years; in 3 years if polyp diameter >1 cm, ≥3 adenomas, sessile, high grade dysplasia, villous

Familial Colon Cancer Syndromes

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

Pathogenesis

- autosomal dominant (AD) inheritance, mutation in APC gene on 5q
- plays a major role in sporadic cancer

Clinical Features

- hundreds to thousands of colonic adenomas by an average age of 40
- extracolonic manifestations
 - carcinoma of duodenum, small bowel, stomach, bile duct, pancreas, thyroid, adrenal
 - congenital hypertrophy of retinal pigment epithelium presents early in life in 2/3 of patients
- virtually 100% lifetime risk of colon cancer (because of number of polyps)
- variants:
 - Gardner's syndrome: FAP + extraintestinal lesions (chiefly bone, desmoid tumours)
 - Turcot's syndrome: FAP + CNS tumours

Investigations

- genetic testing (80-95% sensitive, 99-100% specific)
 - see sidebar for criteria for genetic screening referral
- if no polyposis found: annual flexible sigmoidoscopy from puberty to age 50, then regular screening



Note that rectal cancers have a higher recurrence rate and lower 5-year survival rate than colon cancers. Therefore, do a rectal exam.



Referral Criteria for Genetic Screening for APC

- To confirm the diagnosis of FAP (in patients with ≥100 colorectal adenomas)
- To provide pre-symptomatic testing for individuals at risk for FAP (1st degree relatives who are ≥10 years old)
- To confirm the diagnosis of attenuated FAP (in patients with ≥20 colorectal adenomas)

Treatment

- surgery indicated by age 17-20
- total proctocolectomy with ileostomy or total colectomy with ileorectal anastomosis (needs intensive endoscopic surveillance of rectal stump) or pelvic pouch with ileo-anal anastomosis
- chemotherapy for intra-abdominal desmoids

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC)**Pathogenesis**

- AD inheritance, mutation in a DNA mismatch repair gene resulting in genomic instability and subsequent mutations
- plays a minor role in sporadic cancer

Clinical Features

- early age of onset, right > left colon, synchronous and metachronous lesions
- mean age of cancer presentation is 44 years, lifetime risk 70-80% (greater for men)
- Lynch syndrome I: hereditary site-specific colon cancer
- Lynch syndrome II: cancer family syndrome – high rates of extracolonic tumours (endometrial, ovarian, hepatobiliary, small bowel)

Diagnosis

- diagnosis is clinical – based on Amsterdam Criteria (see sidebar)

Investigations

- genetic testing (80% sensitive) – colonoscopy mandatory even if negative
 - refer for genetic screening individuals who fulfill either the Amsterdam criteria (see sidebar) or revised Bethesda criteria (see sidebar)
- colonoscopy (starting age 20) every 1-2 years
- surveillance for extracolonic lesions (controversial, no guidelines available)

Treatment

- subtotal colectomy and ileosigmoid or ileorectal anastomosis with yearly proctoscopy or sigmoidoscopy

**"Amsterdam" Criteria for HNPCC Diagnosis**

- 3 relatives with colorectal cancer, where one is 1st degree relative of other two
- 2 generations of colorectal cancer
- 1 colorectal cancer before age 50
- FAP is excluded

**Revised Bethesda Criteria – Refer for Genetic Screening for HNPCC**

- Individuals with cancer in families that meet the Amsterdam criteria
- Patients with two HNPCC-related cancers, including synchronous and metachronous colorectal cancer or associated extracolonic cancers (endometrial, ovarian, gastric, hepatobiliary, small bowel, or transitional cell carcinoma of the renal pelvis or ureter)
- Patients with colorectal cancer and a first degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma with one of the cancers diagnosed before age 45 years, and the adenoma diagnosed before age 40 years
- Patients with right-sided colorectal cancer having an undifferentiated pattern (solid/ciriform) on histopathologic diagnosis before age 45 years
- Patients with signet-ring cell type colorectal cancer diagnosed before age 45
- Patients with adenomas diagnosed before age 40

Liver

Investigations of Hepatobiliary Disease

A. TEST OF LIVER FUNCTION**Prothrombin Time (PT or INR)**

- most sensitive marker of hepatic protein synthesis
- increased by:
 - impaired hepatic protein synthesis (>80%) (including all coagulation factors except VIII)
 - vitamin K deficiency; PT reliable marker of liver dysfunction only if vitamin K administration ruled out

Serum Albumin Level

- must exclude malnutrition, renal or GI losses and acute illness

Serum Bilirubin

- marker of hepatic excretion: transport from hepatocyte to bile
- canaliculus breakdown product of hemoglobin; metabolized in the reticuloendothelial system of liver, transported through biliary system, excreted via gut
- direct bilirubin = conjugated; indirect = unconjugated bilirubin
- liver dysfunction causes hyperbilirubinemia (elevated direct bilirubin) since conjugation preserved even in end stage liver failure



All clotting factors except factor VIII and von Willebrand Factor are exclusively synthesized in the liver.

**Serum transaminases >1000 due to**

- Viral hepatitis
- Drugs
- Autoimmune hepatitis
- Hepatic ischemia
- Rarely common bile duct stone



ALT > AST = most causes of hepatitis
 AST > ALT = alcoholic liver disease or other causes of hepatitis that have progressed to advanced cirrhosis
 Alcoholic hepatitis: history of recent alcohol, RUQ abdominal pain, AST/ALT > 2, AST usually < 300, low grade fever, mildly elevated WBC



DDx for Hepatomegaly

- Congestive (right heart failure, Budd-Chiari syndrome)
- Infiltrative
 - Malignant (primary, secondary, lymphoproliferative, leukemia)
 - Benign (fatty liver, cysts, hemochromatosis, extramedullary hematopoiesis, amyloid)
- Proliferative
 - Infectious (viral, tuberculosis, abscess, echinococcus)
 - Inflammatory (granulomas [sarcoid], histiocytosis X)

B. TESTS OF LIVER DAMAGE

- increased AST, ALT = hepatocellular damage
 - ALT more specific to liver; AST from multiple sources (especially muscle)
 - elevation of both highly suggestive of liver injury
 - most common cause of elevated ALT is fatty liver
 - if AST, ALT > 1000, think of acute viral infection, drug-induced liver injury, ischemia (acute congestion or hypotension), autoimmune hepatitis, common bile duct stone (rare)
- increase in ALP and GGT = cholestasis
 - if ALP is elevated alone, rule out bone disease by fractionating ALP
 - obstruction of large duct (common bile duct): extraluminal (pancreatic CA, lymphoma), wall inflammation/stricturing, intraluminal (stones, helminths)
 - ♦ obstruction of microscopic ducts (PBC, PSC)
 - ♦ bile acid transporter defects (drugs, intrahepatic cholestasis of pregnancy)
 - ♦ infiltration of the liver (liver metastases, lymphoma, granulomas, amyloid)

Hepatitis – Acute and Chronic

- see [Infectious Diseases](#), ID18

Etiology

- viral infection
- alcohol
- drugs
- immune-mediated
- toxins



Hepatitis A Virus (HAV)

- RNA virus
- fecal-oral transmission; incubation period 4-6 weeks
- diagnosed by elevated transaminases, positive anti-HAV IgM
- in children: characteristically asymptomatic
- in adults: fatigue, nausea, arthralgia, fever, jaundice
- can cause fulminant hepatic failure and subsequent death (<1-5%)
- can relapse but never becomes chronic



Risk of Developing Infection from a Hollow Needle Puncture

HBV	30%
HCV	3%
HIV	0.3%



Hepatitis B Virus (HBV)

Table 16. Hepatitis B Serology

	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc	Liver Enzymes
Acute HBV	+	–	+	–	IgM	
Chronic HBV (high HBV DNA)	+	–	+	–	IgG	ALT, AST elevated
Chronic HBV (low HBV DNA)	+	–	–	+	IgG	ALT, AST normal
Resolved infection	–	+/-	–	+/-	IgG	
Immunization	–	+	–	–	–	



Causes of Elevated Serum Transaminases in Chronic Hepatitis B

- Ongoing immune mediated liver injury without immune control of HBV
- Reactivation from prior immune control due to lack of adequate immune control
- Seroconversion (HBeAg converting to anti-HBe; spontaneously or with Rx)
- Hepatitis D
- Liver insult (fatty liver, alcohol, drugs, hepatitis A)

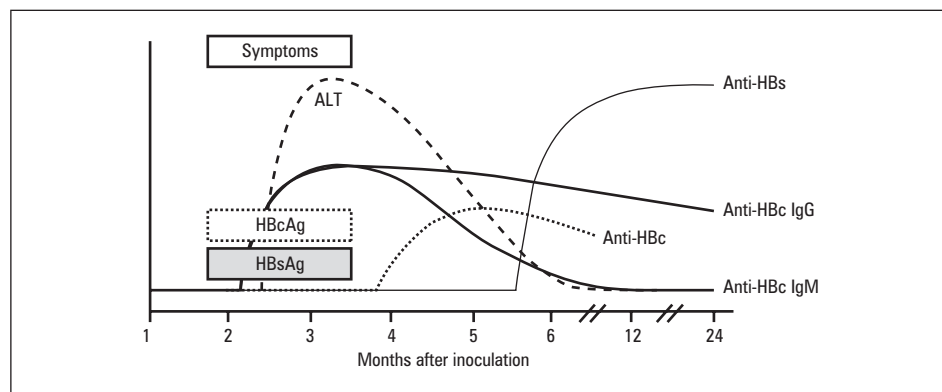


Figure 11. Time Course of Acute Hepatitis B Infection

Epidemiology

- 4 phases of chronic hepatitis B: not all go through all 4 phases but all have positive HBsAg
 - immune tolerance:** extremely high HBV-DNA, HBeAg positive, but normal ALT/AST due to little immune control and minimal immune-mediated liver damage, characteristic of perinatal infection (or 'incubation period' in adult with newly acquired HBV)
 - immune clearance** (or immunoactive): falling HBV DNA levels but still high (>10,000 IU/mL), HBeAg positive, due to immune attack on the virus and immune-mediated liver damage, characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment
 - immune control:** lower HBV-DNA (<10,000 IU/mL, HBeAg negative, anti-HBe positive, ALT/AST normal, due to immune control without immune-mediated liver damage; risk of reactivation to pattern (2) especially with immunosuppression such as corticosteroids, chemotherapy (reactivation clinically resembles acute hepatitis B)
 - reactivation:** "core or precore mutant" = high HBV-DNA >100 IU/ml, HBeAg negative because of pre-core or core promoter gene mutation, anti-HBe positive, ALT/AST high, characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment



- Risk of hepatoma in HBV increases with increasing age, which is likely a surrogate for increasing liver fibrosis/cirrhosis.
- Risk of hepatoma in HCV increases only after cirrhosis develops.

Management

- counselling: 40% of men and 10% of women with perinatal infection will die from HBV-related complications
- if prolonged phase of immune-mediated damage, higher risk of liver fibrosis progression; hepatoma screening with ultrasound q6months if cirrhosis present
 - more likely in men (age >40) and women (age >50)
- consider pharmacological treatment if HBV-DNA >1,000 IU/ml if immune-mediated damage is likely to continue
- treatment goal: reduce serum HBV-DNA to undetectable level to minimize risk of drug resistance/treatment failure
- treatment options: interferon, tenofovir, entecavir, lamivudine, adefovir
- vaccinate against HAV if serology negative
- follow blood and sexual precautions



Without treatment 8-20% of those with ongoing active immune-mediated liver injury can develop cirrhosis within 5 years. In contrast, those in the immune tolerant phase with extremely high HBV-DNA levels are at minimal risk for liver fibrosis as they do not have immune-mediated liver injury.

Hepatitis D

- defective RNA virus requiring HBsAg for entry into hepatocyte, therefore infects only patients with hepatitis B, causes more aggressive disease than hepatitis B virus alone
- co-infection: acquire HDV and HBV together
 - better prognosis than superinfection (acute HDV infection on pre-existing HBV infection)
- HDV can present as fulminant hepatic failure (FHF) and/or accelerate progression to cirrhosis



HDV increases severity of hepatitis but does not increase risk of progression to chronic hepatitis.

Chronic Hepatitis B + D

Management

- low-dose interferon, response only about 20%
- liver transplant for end-stage disease

Hepatitis C Virus (HCV)



- RNA virus
- blood-borne transmission; sexual transmission is "inefficient"
- major risk factor: injection drug use
- other risk factors: blood transfusion received before 1992 (or received in developing world), tattoos, intranasal cocaine use
- clinical manifestation develops 6-8 weeks after exposure
 - symptoms mild and vague (fatigue, malaise, nausea) therefore not commonly diagnosed in acute stage

Diagnosis

- suspected on basis of elevated ALT/AST + positive serum anti-HCV
- diagnosis established by detectable HCV-RNA in serum
- virus genotype correlates with response to treatment but not prognosis
 - serum HCV-RNA inversely correlates with response to treatment
- normal transaminases can have underlying cirrhosis on biopsy, but otherwise excellent prognosis

Management

- blood-borne precautions; vaccinate for hepatitis B and A if serology negative; avoid alcohol
- clearest indication for treatment is subgroup likely to develop clinically significant liver disease: persistently elevated transaminases, liver biopsy shows fibrosis/cirrhosis and at least moderately severe necrosis/inflammation
- indicators of poor response to treatment: cirrhosis, genotype 1, high HCV-RNA, co-infection with HIV, African-American race



HCV treatment lowers the risk of hepatoma.

- alpha interferon + ribavarin aims to clear HCV infection (undetectable HCV-RNA 6 months off treatment that is maintained indefinitely), but only 50-80% success rate and side effects common therefore not all patients treated
 - alpha-interferon SC injection weekly and ribavarin PO BID
- length of treatment determined by time required for HCV-RNA to fall
 - measure HCV-RNA 1 and 3 months after starting treatment
- adverse effects: depression/fatigue, hemolysis, bone marrow suppression (monitor CBC regularly), fevers/myalgia, precipitates autoimmune diseases (rare)

Prognosis

- 80% become chronic; of these 20% evolve to cirrhosis
- risk of hepatoma increases once cirrhosis has developed
- risk factors for liver disease progression are alcohol intake, HIV co-infection, old age at diagnosis
- can cause cryoglobulinemia; associated with membranoproliferative glomerulonephritis, lymphoma

Chronic Hepatitis

Definition

- an increase in serum transaminases for >6 months

Etiology

- fat (metabolic syndrome, alcohol)
- viral (B, B+D, C; not A or E)
- drugs (methyldopa, INH, nitrofurantoin, amiodarone)
- autoimmune
- genetic (hemochromatosis, Wilson's disease, α 1-antitrypsin deficiency)

Clinical Features

- usually asymptomatic, detected incidentally
- increased AST, ALT

Treatment

- treat underlying cause as this will prevent ongoing liver injury and allow recovery

Autoimmune Chronic Active Hepatitis

- diagnosis of exclusion: rule out viruses, drugs, metabolic or genetic causes
- can be severe: 40% mortality at 6 months without treatment
- extrahepatic manifestations
 - sicca, Raynaud's, thyroiditis, Sjögren's, arthralgias
 - hypergammaglobulinemia
 - ♦ anti-smooth muscle antibody elevation is most characteristic; also elevations in anti-LKM (liver kidney microsome, especially in children)
 - less specific: elevated ANA, RF
 - ♦ can have false positive viral serology (especially anti-HCV)
- management: corticosteroids (80% respond) \pm azathioprine (without this most relapse as corticosteroids are withdrawn)

Fulminant Hepatic Failure (FHF)

- in the setting of a previously normal liver, rapid (characteristically <8 weeks) development of jaundice followed by hepatic encephalopathy
- causes: drugs (especially acetaminophen), hepatitis B (measure IgM anti-HBc because sometimes HBV-DNA and even HBsAg rapidly becomes negative), hepatitis A, hepatitis C (rare), ischemic, idiopathic
- management: correct hypoglycemia, monitor level of consciousness, prevent GI bleeding with PPI, vigilant for infection and multiorgan failure (usually requires ICU)
- consider liver biopsy before INR becomes too high
 - chief value is to exclude chronic disease, less helpful for prognosis
- liver transplant: consider early, especially if time from jaundice to encephalopathy >7 days (e.g. not extremely rapid), age <10 or >40, cause is drug or unknown, bilirubin >300 μ mol/L, INR >3.5, creatinine >200 μ mol/L

Table 17. Characteristics of the Viral Hepatitis

Hepatitis	Clinical Presentation	Definition	Communicability	Investigation	Treatment	Prognosis	Complications
Acute Viral Hepatitis	Most subclinical Prodrome: flu-like, may precede jaundice by 1-2 weeks	<6 months	Variable	AST, ALT, ALP, bilirubin	Supportive (hydrate, diet) Hospitalize if: encephalopathy, coagulopathy, severe vomiting, hypoglycemia	Poor prognosis: comorbidities, ↑ Bili, ↑ INR, ↓ Alb, hypoglycemia	Hepatocellular necrosis: AST, ALT > 10-20x normal, ALP and bilirubin minimally ↑, increased cholestasis
Virus	Transmission	Incubation	Communicability	Serology	Management	Prognosis	Complications
Hepatitis A	Fecal-oral	4-6 weeks	2-3 weeks in late incubation to early clinical phase Acute hepatitis in most adults, 10% of children	Anti-HAV (IgM)	General hygiene Treat close contacts (anti-HAV Ig) Prophylaxis for high-risk groups (HAV vaccine ± HAV Ig) unless immune	No chronicity	
Hepatitis B	Parenteral or equivalent Vertical	6 weeks-6 months	HBsAg + state highly communicable Increased during T3 or early post-partum	See Table 16	Prevention: HBV vaccine and/or hepatitis B Ig (HBIG); for needlestick, sexual contact, infants of infected mothers unless already immune	Chronicity in 20%	Hepatocellular carcinoma secondary to cirrhosis Serum sickness-like syndrome Glomerulonephritis Cryoglobulinemia Polyarteritis nodosa Porphyria cutanea tarda
Hepatitis C	Parenteral (transfusion, IDU, sexual [$<$ HBV]) 40% have no known risk factors	6-8 weeks		HCV-RNA Anti-HCV (IgG/IgM)	Prevention: no vaccine Rx: IFN + ribavirin	Chronicity in 80%, 20% of these develop cirrhosis	Hepatocellular carcinoma in 2-5% of cirrhosis per year Cryoglobulinemia
Hepatitis D	Non-parenteral (close contact in endemic areas) Parenteral (blood products, IDU)		Infectious only in presence of HBV (HBsAg required for replication)	HBsAg Anti-HDV (IgG/IgM)	Prevention: HBV vaccine	Predisposes HBV carriers to more severe hepatitis and faster progression to cirrhosis	
Hepatitis E	Fecal-oral (endemic: Africa, Asia, central America, India, Pakistan)	2-6 weeks		Anti-HEV (IgG/IgM)	Prevention: general hygiene, no vaccine	No chronicity	Mild, except in third trimester (10-20% fulminant liver failure)
Chronic Hepatitis	Epidemiology	Time Course	Diagnosis	Management	Prognosis		
Chronic Hepatitis C	50% of chronic hepatitis	At 10 years: chronic hepatitis At 20 years: cirrhosis At 30 years: HCC	Serum HCV-RNA Anti-HCV (+)	Minimize alcohol intake Strict blood precautions Vaccinate for Hep A, B HCC screen with U/S and serum alpha-fetoprotein (AFP) Rx: Pegylated interferon α -2a or 2b + ribavirin	20% progress to cirrhosis 3% of cirrhotics develop HCC		
Chronic Hepatitis B	1-2% of healthy adults with acute hepatitis B 90% if infected at birth	Replicative Phase (HBeAg +): ↑ infectivity Non-reactive Phase (anti-HBe +): ↓ infectivity		Limit alcohol intake Blood/sex precautions HCC screen Rx: interferon, lamivudine, adefovir, entecavir, tenofovir, telbivudine	If HBV-DNA: (-) wam of reactivity (+) wam of progression to cirrhosis		
Chronic Hepatitis B+D				Liver transplant for end-stage disease			

Drug-Induced Liver Disease

Table 18. Classification of Hepatotoxins

	Direct	Indirect
Example	Acetaminophen, CCl ₄	Phenytoin, INH
Dose-dependence	Usual	Unusual
Latent Period	Hours-days	Weeks-months
Host Factors	Not important	Very important
Predictable	Yes	No (idiosyncratic)

Specific Drugs

- acetaminophen
 - metabolized by hepatic cytochrome P450 system
 - can cause FHF (transaminases >1,000 U/L followed by jaundice and encephalopathy)
 - requires 10-15 g in healthy, 4-6 g in alcoholics/anticonvulsant users
 - toxicity
 - mechanism: high acetaminophen dose saturates glucuronidation and sulfation elimination pathway → reactive metabolite is formed → covalently binds to hepatocyte membrane
 - presentation:
 - ♦ first 24 hrs: nausea and vomiting usually within 4-12 hours
 - ♦ 24-48 hrs: asymptomatic but ongoing hepatic necrosis resulting in increased aminotransferases
 - ♦ >48 hrs: continued hepatic necrosis possibly complicated with FHF or resolution
 - ♦ note: potential delay in presentation in sustained-release products
 - blood levels of acetaminophen correlate with the severity of hepatic injury, particularly if time of ingestion known
 - therapy:
 - ♦ gastric lavage/emesis (if <2 hrs after ingestion)
 - ♦ oral activated charcoal
 - ♦ N-acetylcysteine (NAC, Mucomyst®) can be given PO or IV, most effective within 8-10 hours of ingestion, but should be given no matter when time of ingestion
 - promotes hepatic glutathione synthesis
 - ♦ no recorded fatal outcomes if NAC given before increase in transaminases
- chlorpromazine
 - cholestasis in 1% after 4 weeks; often with fever, rash, jaundice, pruritus and eosinophilia
- INH (isoniazid)
 - 20% develop elevated transaminases but <1% develop clinically significant disease
 - susceptibility to injury increases with age
- methotrexate
 - rarely cause cirrhosis, increased risk in the presence of obesity, diabetes, alcoholism (i.e. with underlying risk for pre-existing fatty liver)
 - scarring develops without symptoms or changes in liver enzymes, therefore biopsy may be needed in long-term treatment
- amiodarone
 - can cause same histology and clinical outcome as alcoholic hepatitis
- others
 - azoles, statins, methyl dopa, phenytoin, PTU, rifampin, sulfonamides, tetracyclines
- herbs
 - chaparral, chinese herbs (e.g. germander, comfrey, bush tea)

Wilson's Disease



Definition

- autosomal recessive defect in copper metabolism (gene ATP7B)

Pathology

- impaired transport of copper from hepatic cytoplasm to endoplasmic reticulum, leading to decreased copper available for production of ceruloplasmin and decreased copper excretion via bile excretion

Clinical Manifestations

- liver: cirrhosis, chronic active hepatitis, acute hepatitis, fulminant liver failure, low risk of HCC
- eyes: Kayser-Fleischer rings (copper deposits in Descemet's membrane); more common in patients with CNS involvement, only present in 50% if only liver involvement
- CNS: basal ganglia (wing flapping tremor, Parkinsonism), cerebellum (dysarthria, dysphagia, incoordination, ataxia), cerebrum (psychosis, affective disorder)
- kidneys: Fanconi's syndrome (proximal tubule transport defects) and stones
- blood: intravascular hemolysis; may be initial presentation in fulminant hepatitis
- joints: arthritis, bone demineralization, calcifications

Investigations

- suspect if increased liver enzymes with clinical manifestations at young age (<30); especially combination of liver disease with trauma, dystonia, psychiatric symptoms
- screening tests:
 1. reduced serum ceruloplasmin (<50% of normal)
 2. Kayser-Fleischer rings (usually require slit-lamp examination)
 3. increased urinary copper excretion
- gold standard:
 1. increased copper on liver biopsy by quantitative assay
 2. genetic analysis imperfect as many mutations in ATP7B are possible

Treatment

- chelators (penicillamine, trientine): increased urinary excretion of copper
- tetrathiomolybdate preferred if neurological involvement
- zinc acetate
 - blocks intestinal absorption of copper
 - sequesters excess copper
- screen relatives
- liver transplant in severe cases



Clinical Manifestations of Wilson's Disease

ABCD

Asterixis
Basal ganglia degeneration: suspect if parkinsonian features in the young
Ceruloplasmin ↓
Cirrhosis
Corneal deposits (KF ring)
Copper
Dementia

Hemochromatosis



Definition

- excess iron storage, which causes multiorgan system dysfunction with total body stores of iron increased to 20-40 g (normal 1 g)

Etiology

- primary hemochromatosis
 - due to common recessive gene (HFE, 5%); 1/400 patients are homozygotes
 - results in ongoing gut absorption of iron despite adequate iron stores
- secondary hemochromatosis
 - parenteral iron overload (e.g. transfusions)
 - chronic hemolytic anemia: thalassemia, pyruvate kinase deficiency
 - excessive iron intake



Not 100% penetrant: not all with homozygous gene defect have clinical iron overload.

Clinical Features

- usually presents with trivial elevation in serum transaminases
- liver: cirrhosis (30%), HCC (200x increased risk) – most common cause of death (1/3 of patients)
- pancreas: diabetes, chronic pancreatitis
- skin: bronze or grey (due to melanin, not iron)
- heart: dilated cardiomyopathy
- pituitary: hypogonadotropic hypogonadism (impotence, decreased libido, amenorrhea)
- joints: arthralgia (any joint but especially MCP joints), chondrocalcinosis

Investigations

- screening for individuals with clinical features and/or family history (1/4 chance of sibling having the disease)
 - transferrin saturation (free Fe/TIBC) >50%
 - serum ferritin >400 ng/ml
 - HFE gene analysis: 90% of idiopathic hemochromatosis have homozygous C282Y gene mutation
- liver biopsy (to define degree of iron overload and to detect cirrhosis)
 - usually indicated if age >40, elevated ALT/AST, or ferritin >1000
- HCC screening if cirrhosis



Ferritin may never normalize if other causes of high ferritin present (e.g. fatty liver from metabolic syndrome or alcohol).

Treatment

- phlebotomy: weekly or q2weeks then lifelong maintenance phlebotomies q2-6 months
- deferoxamine if phlebotomy contraindicated (e.g. cardiomyopathy, anemia)
- primary hemochromatosis responds well to phlebotomy
- secondary hemochromatosis usually requires chelation therapy

Prognosis

- normal life expectancy if treated before the development of cirrhosis or diabetes



Alcoholic Liver Disease



13 g ethanol = 1 beer = 4 oz wine = 1.5 oz liquor

Types of Lesions

- fatty liver (all alcoholics): always reversible if alcohol stopped
- alcoholic hepatitis (35% of alcoholics): usually reversible if alcohol stopped
- cirrhosis (10-15% of alcoholics): potentially irreversible

Pathophysiology

- several mechanisms, poorly understood
- ethanol oxidation to acetaldehyde:
 - reduces NAD to NADH; increased NADH decreases ATP supply to liver, impairing lipolysis so fatty acid and triglycerides accumulate in liver
 - binds to hepatocytes evoking an immune reaction
- ethanol increases gut permeability leading to increased bacterial translocation
- alcohol metabolism causes:
 - relative hypoxia in liver zone III > zone I
 - necrosis and hepatic vein sclerosis
- histology of alcoholic hepatitis:
 - ballooned (swollen) hepatocytes often containing Mallory bodies, characteristically surrounded by neutrophils
 - large fat globules
 - fibrosis: space of Disse and perivenular



Biopsy + Histology of Alcoholic Hepatitis (triad)

- Hepatocyte necrosis with surrounding inflammation in zone III
- Mallory bodies (intracellular eosinophilic aggregates of cytokeratins)
- Chicken-wire fibrosis (network of intralobular connective tissue surrounding cells and venules)



GI Complications of Alcohol Abuse

Esophagus

- Mallory-Weiss tear
- Esophageal varices (secondary to portal hypertension)

Stomach

- Alcoholic gastritis

Pancreas

- Acute pancreatitis
- Chronic pancreatitis

Liver

- Alcoholic hepatitis
- Fatty liver
- Cirrhosis
- Hepatic encephalopathy
- Portal hypertension (secondary to cirrhosis)
- Ascites (secondary to cirrhosis)
- HCC (secondary to cirrhosis)

Clinical Features

- threshold for cirrhosis is >20-40 g EtOH/day in females or >40-80 g EtOH/day in males x 10-20 years; cirrhosis develops in about 5% of those who consume this amount daily on a continuous basis; cirrhosis risk increases with amount of alcohol consumed above threshold
- clinical findings do not predict type of liver involvement
- fatty liver:
 - mildly tender hepatomegaly; jaundice rare
 - mildly increased transaminases <5x normal
- alcoholic hepatitis:
 - variable severity: mild to fatal liver failure
 - mild: stops drinking because feels unwell, resumes when feeling better (if assessed, findings of hepatitis, potentially mild jaundice and mildly elevated INR)
 - severe: stops drinking but feels unwell, low grade fever, RUQ discomfort – mimics RLL pneumonia and cholecystitis
- blood tests are non-specific, but in general:
 - AST:ALT > 2:1 (usually <300)
 - increased GGT
 - CBC: increased MCV (mean corpuscular volume), increased WBC
- prognosis determined by degree of liver failure (INR elevation, bilirubin elevation)

Treatment

- alcohol cessation (see [Psychiatry](#), PS20)
 - Alcoholics Anonymous, disulfiram, naltrexone, acamprosate
- multivitamin supplements (especially thiamine)
- caution with drugs metabolized by the liver
- prednisone 40 mg OD x 28 days (no taper) in subgroup with elevated bilirubin and INR, or if encephalopathy; but contraindicated if GI bleeding, renal failure, infection
- pentoxifylline decreases TNF, shown in one trial to reduce renal failure but not mortality in alcoholic hepatitis, now widely used due to favourable side effect profile

Prognosis

- fatty liver: complete resolution with cessation of EtOH intake
- alcoholic hepatitis mortality
 - immediate: 30%-60% in the first 6 months if severe
 - with continued alcohol: 70% in 5 years
 - with cessation: 30% in 5 years

Non-Alcoholic Fatty Liver Disease (NAFLD)

Etiology/Epidemiology

- spectrum of disorders characterized by macrovesicular hepatic steatosis
- most common cause of liver disease in North America

Pathophysiology

- pathogenesis not well elucidated; insulin resistance implicated as key mechanism, leading to hepatic steatosis
- changes indistinguishable from those of alcoholic hepatitis despite negligible history of alcohol consumption

Risk Factors

- likely a component of the metabolic syndrome along with type II diabetes, hypertension, hypertriglyceridemia
- rapid weight loss or weight gain

Clinical Features/Investigations

- often asymptomatic
- may present with fatigue, malaise and vague RUQ discomfort
- elevated serum triglyceride/cholesterol levels and insulin resistance
- elevated serum AST, ALT \pm ALP; AST/ALT <1
- presents as echogenic liver texture on ultrasound
- liver biopsy diagnostic but often necessary only for prognosis

Management

- no proven effective therapy other than gradual weight loss
- modification of risk factors is generally recommended, particularly gradual weight reduction
- optimization of therapy for diabetes, hyperlipidemia, hypertension likely helpful

Prognosis

- better prognosis than alcoholic hepatitis
 - $<25\%$ progress to cirrhosis over a 7-10 year period
- risk of progression increases if inflammation or scarring alongside fat infiltration (non-alcoholic steatohepatitis)
- other clinical indicators of unfavourable prognosis: diabetes, age

Cirrhosis

Definition

- liver damage characterized by diffuse distortion of the basic architecture and replacement with scar tissue
- Stage 1 cirrhosis is compensated and asymptomatic, can last for 10-20 years with almost normal life expectancy
- Stage 2 cirrhosis is the onset of first decompensation, typically development of liver failure, ascites or variceal bleed



Fibrosis may regress and disappear if cause of liver injury is treated or resolves.



Usual causes of death in cirrhosis: renal failure (hepatorenal syndrome), sepsis, GI bleed, or HCC.

Etiology

- fatty liver (alcohol, metabolic syndrome)
- chronic viral hepatitis (B, B+D, C; not A or E)
- autoimmune hepatitis
- hemochromatosis
- α 1-antitrypsin deficiency
- primary biliary cirrhosis
- chronic hepatic congestion
 - cardiac cirrhosis (chronic right heart failure, constrictive pericarditis)
 - hepatic vein thrombosis (Budd-Chiari)
- idiopathic
- rare – Wilson's disease, Gaucher's disease

Diagnosis

- definitive diagnosis is histologic (liver biopsy)
- other tests may be suggestive:
 - blood work: fall in platelet count <150 is the earliest finding, followed many years later with rise in INR, fall in albumin, rise in bilirubin, fall in glucose level (pre-terminal event)
 - imaging:
 - ♦ U/S is the primary imaging modality but only finds advanced cirrhosis
 - ♦ CT to look for varices, nodular liver texture, splenomegaly, ascites
 - gastroscopy: varices or portal gastropathy

Management

- treat underlying disorder
- decrease insults (e.g. alcohol cessation, hepatotoxic drugs)
- follow patient for complications (esophageal varices, ascites, HCC defines stage 2 cirrhosis)
- prognosis: Child-Pugh Score (see Table 19)
- liver transplantation for end-stage disease if no alcohol for >6 months; use MELD stratification
 - MELD (Model for End Stage Liver Disease)
 - ♦ used to stratify patients on transplant list
 - ♦ score <14 predicts 3 month survival
 - ♦ based on creatinine, INR and total bilirubin

Table 19. Child-Pugh Score and Interpretation

Classification	1	2	3
Serum bilirubin (μ mol/L)	<34	34-51	>51
Serum albumin (g/L)	>35	28-35	<28
Presence of ascites	Absent	Controllable	Refractory
Encephalopathy	Absent	Minimal	Severe
INR	<1.7	1.7-2.3	>2.3
Interpretation			
Points	Class	Life Expectancy	Perioperative Mortality
5-6	A	15-50 years	10%
7-9	B	Candidate for transplant	30%
10-15	C	1-3 months	82%
Score: 5-6 (Child's A), 7-9 (Child's B), 10-15 (Child's C)			

*Note: Child's classification is rarely used for shunting, but is still useful to quantitate the severity of cirrhosis

Complications

- hematologic changes in cirrhosis
 - pancytopenia from hypersplenism: platelets first, then WBC, then hemoglobin
 - decreased clotting factors resulting in elevated INR, thus tendency for bruising and bleeding
- renal failure in cirrhosis
 - classifications
 - ♦ pre-renal (usually due to over-diuresis)
 - ♦ acute tubular necrosis (ATN)
 - ♦ hepatorenal syndrome (HRS)
 - Type I: sudden and acute renal failure in the setting of pre-existing type II HRS
 - Type II: gradual increase in creatinine with worsening liver function
 - e.g. creatinine doubling over years
 - hepatorenal syndrome can occur at any time in severe liver disease, especially after:
 - ♦ overdiuresis or dehydration, such as diarrhea, vomiting, etc.
 - ♦ GI bleed
 - ♦ sepsis



Cirrhosis Complications

VARICES

Varices
Anemia
Renal failure
Infection
Coagulopathy
Encephalopathy
Sepsis

- hepatorenal syndrome vs. pre-renal failure – difficult to differentiate:
 - ♦ similar blood and urine findings, (see [Nephrology](#), NP19)
 - ♦ urine sodium very low in hepatorenal; low in prerenal
 - ♦ intravenous fluid challenge (giving volume expanders improves prerenal failure but not hepatorenal syndrome)
 - ♦ treatment for hepatorenal syndrome is generally unsuccessful at improving long term survival
 - ♦ octreotide + midodrine + albumin (increased renal blood flow by increased systemic vascular resistance)
 - ♦ definitive treatment is liver transplant
- hepatopulmonary syndrome (HPS)
 - clinical triad:
 1. liver disease
 2. increased alveolar-arterial gradient while breathing room air
 3. evidence for intrapulmonary vascular abnormalities
 - majority of cases due to cirrhosis, though can be due to other chronic liver diseases, such as non-cirrhotic portal hypertension
 - thought to arise from ventilation-perfusion mismatch, intrapulmonary shunting and limitation of oxygen diffusion, failure of damaged liver to clear circulating pulmonary vasodilators, vs. production of a vasodilating substance by the liver
 - clinical features:
 - ♦ hyperdynamic circulation with cardiac output >7 L/min at rest and decreased pulmonary + systemic resistance (intrapulmonary shunting)
 - ♦ dyspnea, platypnea (increase in dyspnea in upright position, improved by recumbency) and orthodeoxia (desaturation in the upright position, improved by recumbency)
 - ♦ diagnosis via contrast-enhanced (inject air bubbles into peripheral vein) echocardiography (air bubbles appear in left ventricle after third heartbeat; normal = no air bubbles; in ventricular septal defect air bubbles seen <3 heartbeats)
 - ♦ only proven treatment is liver transplantation

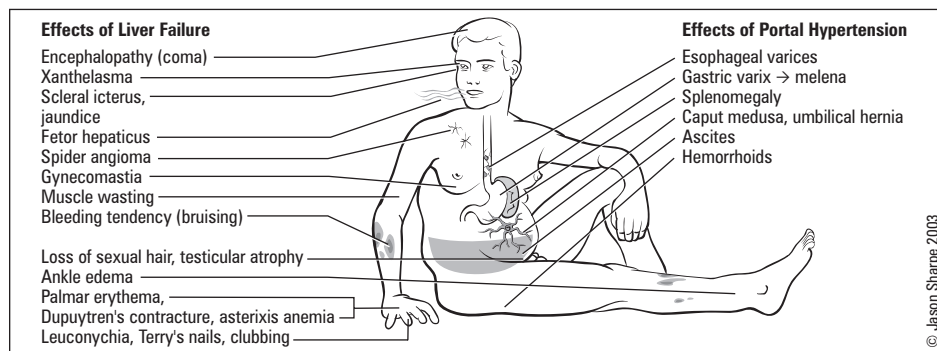


Figure 12. Clinical Features of Liver Disease

Hepatocellular Carcinoma (HCC)

- see [General Surgery](#), GS42

Liver Transplant

- see [General Surgery](#), GS44

Portal Hypertension

Definition

- pressure gradient between hepatic vein pressure and wedged hepatic vein pressure (corrected sinusoidal pressure) >5 mmHg

Pathophysiology

- 3 sites of increased resistance (remember pressure = flow x resistance)
 - pre-sinusoidal (e.g. portal vein thrombosis, schistosomiasis, sarcoidosis)
 - sinusoidal (e.g. cirrhosis, alcoholic hepatitis)
 - post-sinusoidal (e.g. right-sided heart failure, hepatic vein thrombosis, veno-occlusive disease, constrictive pericarditis)

**Portal Hypertension****Signs**

Esophageal varices
Melena
Splenomegaly
Ascites
Hemorrhoids

Management

β -blockers
Nitrates
Shunts [e.g. transjugular intrahepatic portosystemic shunt (TIPS)]

Complications

- GI bleeding from varices in esophagus, less commonly in stomach, even less frequently from portal hypertensive gastropathy
- ascites
- hepatic encephalopathy
- thrombocytopenia
- renal dysfunction
- sepsis
- arterial hypoxemia

Management

- β -blockers (propranolol, nadolol) decreases risk of bleeding from varices
- transjugular intrahepatic portosystemic shunt (TIPS): to decrease portal venous pressure
 - shunt between portal and hepatic vein via percutaneous puncture of portal vein, and (central) hepatic vein via transjugular vein catheterization
 - can be used to stop acute bleeding or prevent rebleeding or treat ascites
 - shunt usually remains open for <1 year
 - complications: hepatic encephalopathy, deterioration of hepatic function
 - contraindicated with severe liver dysfunction
- other surgically created shunts (rare): portocaval, distal spleno-renal (Warren shunt)

**Hepatic Encephalopathy****Definition**

- acute neuropsychiatric syndrome secondary to liver disease

Pathophysiology

- porto-systemic shunt around hepatocytes and decreased hepatocellular function increases toxin (believed to be ammonia from gut, mercaptans, fatty acids, amino acids) delivery to brain

Precipitating Factors

- nitrogen load (GI bleed, protein load from food intake, renal failure, constipation)
- drugs (narcotics, CNS depressants)
- electrolyte disturbance (hypokalemia, alkalosis, hypoxia, hypovolemia)
- infection (spontaneous bacterial peritonitis)
- deterioration in hepatic function or superimposed liver disease

Stages

- I: apathy, restlessness, reversal of sleep-wake cycle, slowed intellect, impaired computational abilities, impaired handwriting
- II: asterixis, lethargy, drowsiness, disorientation
- III: stupor (rousable), hyperactive reflexes, extensor plantar responses
- IV: coma (response to painful stimuli only)

Investigations

- clinical diagnosis: supported by laboratory findings and exclusion of other neuropsychiatric diseases
- rule out:
 - non-liver-related neuropsychiatric disease in a patient with liver problems (e.g. alcohol withdrawal or intoxication, sedatives, subdural hematoma, metabolic encephalopathy)
 - causes of metabolic encephalopathy (e.g. renal failure, respiratory failure, severe hyponatremia, hypoglycemia)
- characteristic EEG findings: diffuse (non-focal), slow, high amplitude waves

Treatment

- treat underlying precipitating factors
- decrease generation of nitrogenous compounds
 - decrease dietary protein to 50 g/day; vegetable protein is better tolerated than animal protein
 - lactulose: titrated to achieve 2 to 3 soft stools per day
 - ♦ prevents diffusion of NH_3 (ammonia) from the colon into blood by lowering pH and forming non-diffusible NH_4 (ammonium)
 - ♦ serves as a substrate for incorporation of ammonia by bacteria, promotes growth in bowel lumen of bacteria which produce minimal ammonia
 - ♦ also acts as a laxative to eliminate nitrogen-producing bacteria from colon
- if inadequate response with lactulose, may try antibiotics
 - broad-spectrum antibiotics (metronidazole, rifaximin) eliminate ammonia producing bacteria from bowel lumen
- avoid causing severe diarrhea with lactulose to decrease fluid/electrolyte problems
- best acute treatment in comatose patient is tap water enemas

**Precipitating Factors for Hepatic Encephalopathy****Hepatics**

Hemorrhage in GI tract/Hypokalemia
Excess dietary protein
Paracentesis
Alkalosis/Anemia
Trauma
Infection
Colon surgery
Sedatives

Ascites

Definition

- accumulation of excess fluid in the peritoneal cavity

Etiology

Table 20. Serum-Ascites Albumin Gradient as an Indicator of the Causes of Ascites

Serum [Alb] – Ascitic [Alb] >11 g/L (1.1 g/dL) Portal Hypertension Related	Serum [Alb] – Ascitic [Alb] <11 g/L (1.1 g/dL) Nonportal Hypertension Related
Cirrhosis/severe hepatitis	Peritoneal carcinomatosis
Chronic hepatic congestion (right heart failure, Budd-Chiari)	TB
Massive liver metastases	Pancreatic disease
Myxedema	Serositis
	Nephrotic syndrome*

* In nephrotic syndrome: decreased serum [Alb] to begin with therefore gradient not helpful

Pathogenesis

- increased portal pressure and low oncotic pressure (e.g. low serum albumin) drives sodium/water out of the splanchnic portal circulation into abdominal cavity
- key factor in pathogenesis is increased sodium (and water) retention by the kidney
 - “underfill hypothesis”: circulation underfilling because of fluid leaving circulation (secondary to high portal pressure, low oncotic pressure)
 - “overflow hypothesis”: direct effect of cirrhosis on kidney
 - peripheral arteriolar vasodilation theory: incorporates both theories (most popular)
- cirrhosis via unknown factors causes splanchnic vasodilation via nitric oxide, increasing vascular capacitance, which is underfilled relative to its capacity, but overfilled as compared to before the onset of vasodilation (i.e. volume to capacitance ratio low, but absolute volume is high)

Diagnosis

- abdominal ultrasound
- physical exam (clinically detectable when >500ml):
 - bulging flanks, shifting dullness, fluid-wave test positive
 - most sensitive sign: ankle swelling

Investigations

- diagnostic paracentesis
 - 1st aliquot: cells and differential
 - 2nd aliquot: chemistry (esp. albumin, but also protein, amylase if pancreatitis, TG if turbid and suspect chylous ascites)
 - 3rd aliquot: C&S, Gram stain
 - 4th aliquot: cytology (usually positive in peritoneal carcinomatosis)

Treatment

- for non-refractory ascites:
 - Na restriction (daily sodium intake <2 grams)
 - diuretics: spironolactone, furosemide
 - aim for daily weight loss 0.5-1 kg if concomitant peripheral edema (which is mobilized quicker than ascitic fluid), more rapid weight loss increases risk of renal failure
 - double diuretic dose every 2-4 weeks to achieve aim
- for refractory ascites (diuretics inadequate or intolerated):
 - therapeutic paracentesis indicated
 - IV albumin (not indicated if <5 L removed by paracentesis)
 - TIPS usually provides temporary benefit but no survival benefit
 - liver transplantation should be considered in every case, since development of ascites in cirrhosis indicates 50% death rate in 3 years

Complication: Bacterial Peritonitis

- primary/spontaneous bacterial peritonitis (SBP)
 - complicates ascites, does not cause it (occurs in 10% of cirrhotic ascites), higher risk in GI bleed
 - 1/3 of patients are asymptomatic, thus do not hesitate to do a diagnostic paracentesis in ascites even if no clinical indication of infection
 - fever, chills, abdominal pain, ileus, hypotension, worsening encephalopathy
 - Gram-negatives compose 70% of pathogens: *E. coli* (most common), *Streptococcus*, *Klebsiella*



Secondary bacterial peritonitis (as opposed to primary bacterial peritonitis) usually results from a perforated viscus or surgical manipulation.

Primary Prophylaxis of Spontaneous Bacterial Peritonitis Delays Hepatorenal Syndrome and Improves Survival in Cirrhosis

Gastroenterology 2007; 133:818-24.

Study: RCT, double-blinded study with 1 year follow-up.

Population: 68 patients with cirrhosis, ascites, ascitic fluid protein <15 g/L and impaired renal function or severe liver failure.

Intervention: General, regional or combined anesthesia to patients undergoing a surgical procedure.

Main Outcome: Norfloxacin versus placebo.

Results: There was a significant reduction of patients developing spontaneous bacterial peritonitis SBP (6% vs. 30%, $p=0.02$) and spontaneous bacteremia (0% vs. 12%, $p=0.05$) with norfloxacin therapy. There were significantly fewer patients who developed all-cause renal failure (7 vs. 16, $p=0.03$) and hepatorenal syndrome with norfloxacin therapy. Probability of survival at 3 months (94% vs. 62%, $p=0.02$) and 1 year (60% vs. 48%, $p=0.003$) were high in patients treated with norfloxacin.

Conclusion: Primary prophylaxis with norfloxacin in patients with advanced cirrhosis reduced SBP, HRS, and improved 1 year survival.

- diagnosis
 - absolute neutrophil count in peritoneal fluid $>0.25 \times 10^9$ cells/L (250 cells/mm³) or WBC count $>0.5 \times 10^9$ cells/L (500 cells/mm³)
 - Gram stain positive in only 10-50% of patients
 - culture positive in <80% of patients (not needed for diagnosis)
- treatment
 - IV antibiotics (cefotaxime 2 g q12 h is the treatment of choice for 5-10 days; modify if response inadequate, culture shows resistant organisms)
 - prophylaxis long-term indicated after recovery from one episode of SBP, prophylaxis short term if GI bleeding in cirrhosis, with daily norfloxacin or TMP-SMX for 5-7 days may decrease the frequency of recurrent SBP, use if GI bleeding/previous SBP
 - IV albumin (1.5 g/kg first dose, 1 g/kg day 3) decreases mortality by lowering risk of acute renal failure

Biliary Tract

Jaundice

- see Table 21, Figures 13 and 14

Signs and Symptoms

- dark urine, pale stools – suggests that bilirubin elevation is from direct fraction
- pruritus – suggests chronic disease
- abdominal pain – suggests biliary tract obstruction from stone or pancreatic tumour (obstructive jaundice)
- painless jaundice – think of pancreatic cancer

Investigations

- blood work: CBC, bilirubin (direct and total), liver enzymes (AST, ALT, ALP, GGT), liver function tests (INR/PT, PTT, albumin), amylase
- U/S for evidence of bile duct obstruction (e.g. bile duct dilation)
- direct bile duct visualization
 - magnetic resonance cholangiopancreatography (MRCP) – non-invasive
 - endoscopic retrograde cholangiopancreatography (ERCP) – invasive, most accurate, allows for therapeutic intervention
 - percutaneous transhepatic cholangiography (PTC) – if ERCP fails, if obstruction is in liver

Table 21. Classification of Jaundice

I. Predominantly Unconjugated Hyperbilirubinemia

1. Overproduction
 - Hemolysis
 - Ineffective erythropoiesis (megaloblastic anemias, others)
2. Decreased hepatic uptake
 - Gilbert's syndrome
 - Drugs (e.g. rifampin)
3. Decreased conjugation
 - Drug inhibition (e.g. chloramphenicol)
 - Crigler-Najjar syndromes type I and II
 - Neonatal jaundice
 - Gilbert's syndrome

II. Predominantly Conjugated Hyperbilirubinemia

1. Impaired hepatic secretion
 - Familial disorders (e.g. Rotor syndrome, Dubin-Johnson syndrome, cholestasis of pregnancy)
 - Hepatocellular disease – by far the most common
 - Drug-induced cholestasis (e.g. oral contraceptives, chlorpromazine)
 - Primary biliary cirrhosis (PBC)
 - Primary sclerosing cholangitis (PSC)
 - Sepsis
 - Post-operative
2. Extrahepatic biliary obstruction
 - Intraductal obstruction
 - Gallstones
 - Biliary stricture
 - Parasites
 - Malignancy (cholangiocarcinoma)
 - Sclerosing cholangitis
 - Extraductal obstruction
 - Malignancy (e.g. pancreatic cancer, lymphoma)
 - Metastases in peri-portal nodes
 - Inflammation (e.g. pancreatitis)

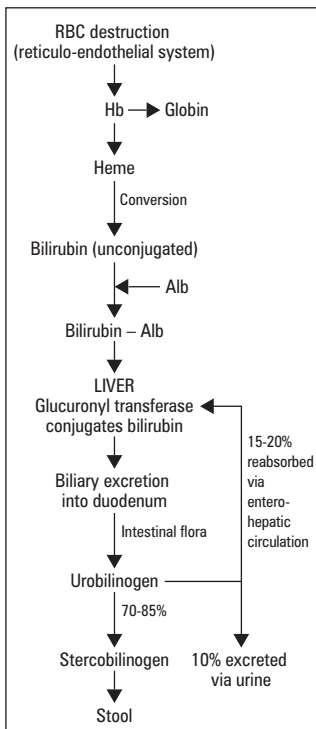


Figure 13. Production and Excretion of Bilirubin

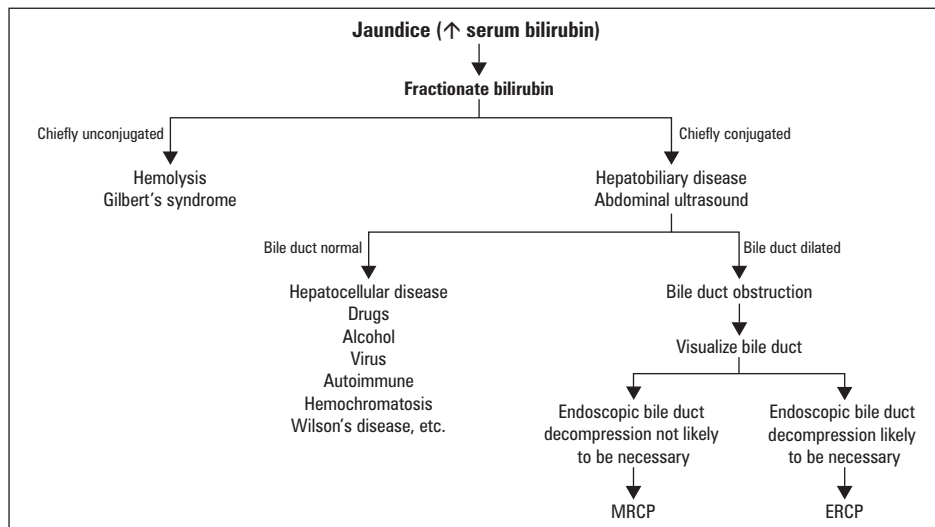


Figure 14. Approach to Jaundice

Gilbert's Syndrome

Definition

- mild decrease in glucuronyltransferase activity leading to defective conjugation of bilirubin

Etiology/Epidemiology

- some patients have decreased hepatobiliary uptake
- affects 7% of population, especially males
- autosomal dominant, 70% due to a mutation in the UGT gene

Signs and Symptoms

- presents in teens-20s, often an incidental finding
- only manifestation is intermittent jaundice with increased serum unconjugated bilirubin developing most characteristically while fasting; no other clinical implications

Treatment

- none indicated (entirely benign)



Gilbert's Syndrome vs. Crigler-Najjar Syndrome

Gilbert's Syndrome: mild decrease in glucuronyltransferase activity

Crigler-Najjar Syndrome: complete deficiency of glucuronyltransferase

Sclerosing Cholangitis

Definition

- inflammation of biliary tree (intra and/or extrahepatic bile ducts) leading to scarring and obliteration

Etiology

- primary/idiopathic
 - most common
 - associated with IBD in up to 70% (usually male)
 - one of the most common indications for transplant
- secondary – less common
 - long-term choledocholithiasis
 - cholangiocarcinoma
 - surgical/traumatic injury (iatrogenic)
 - contiguous inflammatory process
 - post-ERCP
 - associated with HIV/AIDS (“HIV cholangiopathy”)

Signs and Symptoms

- often insidious, may present with fatigue and pruritus
- may present with signs of episodic bacterial cholangitis secondary to biliary obstruction

**ERCP**

- Absence of narrowing in PBC
- Narrowing of intra and extrahepatic ducts in PSC

Diagnosis

- increased ALP (hallmark), less often increased bilirubin
- mildly increased AST, usually <300 U/L
- p-ANCA (30-80%), elevated IgM (40-50%)
- ERCP shows narrowing of bile ducts, both intrahepatic and extrahepatic bile ducts
 - if intrahepatic narrowing only, do antimitochondrial antibody to rule out PBC

Complications

- repeated bouts of cholangitis may lead to complete biliary obstruction with resultant secondary biliary cirrhosis and hepatic failure
- increased incidence of cholangiocarcinoma (10-15%): difficult to diagnose and treat

Management

- image bile duct (MRCP) at least annually for early detection of cholangiocarcinoma
- endoscopic sphincterotomy, biliary stent in selected cases of dominant CBD stricture
- antibiotics for cholangitis
- suppurative cholangitis requires emergency drainage of pus in CBD
- liver transplantation appears the best treatment for advanced sclerosing cholangitis (nearly 90% 1 year survival; mean follow-up from time of diagnosis to need for transplant is 10 years)
- ursodiol (previously recommended) may actually increase mortality

Prognosis

- unfavourable regardless of treatment
- mean survival after diagnosis remains 4-10 years

Primary Biliary Cirrhosis (PBC)

Definition

- chronic inflammation and fibrous obliteration of intrahepatic bile ductules

Etiology/Epidemiology

- likely autoimmune (associated with Sjögren's syndrome, scleroderma, CREST syndrome, RA, thyroiditis)
- affects mainly middle-aged women (M:F = 1:9)

Signs and Symptoms

- often asymptomatic
- earliest symptoms: pruritus, fatigue
- after several months-years: jaundice and melanosis (darkening skin) and other signs of cholestasis
- eventually: hepatocellular failure, portal hypertension, ascites
- high incidence of osteoporosis

Investigations

- increased ALP, GGT; bilirubin rises in later stage
- positive anti-mitochondrial antibodies (AMA) (95% specificity)
- increased serum cholesterol → xanthelasma, xanthomas (mild increase in LDL, larger increase in HDL)
- liver biopsy confirms diagnosis and stages severity
- normal bile duct on MRCP rules out bile duct obstruction which can mimic PBC
- recently described "overlap" syndromes with autoimmune cholangitis, autoimmune hepatitis, sclerosing cholangitis

Clinical Course

- can be fatal, although not all asymptomatic patients show progression

Treatment

- treat with ursodiol (less frequently colchicine, methotrexate)
- cholestyramine (for pruritus and hypercholesterolemia)
- calcium and vitamin D for low bone density; bisphosphonates if osteoporosis severe
- monitor for thyroid disease
- liver transplant if disease severe, progressive

Table 22. Primary Sclerosing Cholangitis vs. Primary Biliary Cirrhosis

	Primary Sclerosing Cholangitis	Primary Biliary Cirrhosis
Predominant Gender	Male	Female
Associated Comorbidities	IBD Colitis	Other autoimmune disorders (Sjögren's, CREST, RA)
Affected Ducts	Both intra- and extra-hepatic	Intrahepatic only
Investigations	ERCP/MRCP (narrowing of ducts visualized)	Anti-mitochondrial antibodies, IgM, increased lipids, liver biopsy (absence of duct narrowing on ERCP)

Secondary Biliary Cirrhosis

Definition

- cirrhosis from prolonged partial or total obstruction of major bile ducts

Etiology

- acquired: post-op strictures, chronic pancreatitis, sclerosing cholangitis, stone in bile duct
- congenital: cystic fibrosis (CF), congenital biliary atresia, choledochal cysts

Diagnosis

- cholangiography and liver biopsy

Treatment

- treat obstruction, give antibiotics for cholangitis prophylaxis

Ascending Cholangitis

Definition

- infection of the biliary tree

Etiology

- stasis in the biliary tract due to obstruction or stricture (usually from previous cholecystectomy)
- infection originates in the duodenum or spreads hematogenously from the portal vein
- bacteria
 - *E. coli*, *Klebsiella*, *Enterobacter*, *Enterococcus*
 - co-infection with *Bacteroides* and *Clostridia* can occur

Signs and Symptoms

- Charcot's Triad: fever, RUQ pain, jaundice (50-70%)
- Reynold's Pentad in patients with suppurative cholangitis: fever, RUQ pain, jaundice, hypotension, confusion

Diagnosis

- increased WBC
- usually increased ALP, ALT, less often increased bilirubin
- blood culture
- abdominal U/S – CBD dilation, stones

Treatment

- antibiotic therapy – broad spectrum to cover Gram-negatives and *Enterococcus*
 - ampicillin + gentamicin OR 3rd generation cephalosporin OR imipenem
 - consider metronidazole to cover anaerobes, especially if previous CBD manipulation
- ERCP – diagnosis and therapeutic sphincterotomy, stone extraction

Prognosis

- good with effective drainage and antibiotics in mild to moderate cases
- high mortality (~50%) in patients with Reynold's Pentad



Charcot's Triad

- RUQ pain
- Fever
- Jaundice



Reynold's Pentad

- Charcot's triad
- Hypotension
- Confusion

Pancreas

Pancreatic Enzyme Abnormalities



Pancreatic Enzymes

- Amylase
- Lipase
- Trypsin
- Chymotrypsin



When serum amylase >5x normal, the cause is almost always pancreatitis or renal disease.

Causes of Increased Serum Amylase

- pancreatic disease
 - pancreatitis, pancreatic duct obstruction (e.g. ampullary cancer), pseudocyst, abscess, ascites, trauma, cancer
- non-pancreatic abdominal disease
 - biliary tract disease, bowel obstruction/ischemia, perforated or penetrating ulcer, ruptured ectopic pregnancy, aneurysm, chronic liver disease, peritonitis
- non-abdominal disease
 - cancer (lung, esophagus, etc.), salivary gland lesions, bulimia, renal transplant/insufficiency, burns, ketoacidosis
 - macroamylasemia

Causes of Increased Serum Lipase

- pancreatic disease: same as above
- non-pancreatic abdominal disease (mild elevations only): same as above
- non-abdominal disease
 - macrolipasemia
 - renal failure



Acute Pancreatitis



When thinking about the causes of acute pancreatitis remember: **I GET SMASHED**, but vast majority due to gallstones or ethanol

Etiology

Idiopathic: thought to be hypertensive sphincter or microlithiasis

Gallstones (45%)

Ethanol (35%)

Tumours: pancreas, ampulla, choledochocoele

Scorpion stings

Microbiological

- bacterial: *Mycoplasma*, *Campylobacter*, TB, *M. avium intracellulare*, *Legionella*, leptospirosis
- viral: mumps, rubella, varicella, viral hepatitis, CMV, EBV, HIV, Coxsackie virus, echovirus, adenovirus
- parasites: ascariasis, clonorchiasis, echinococcosis

Autoimmune: SLE, polyarteritis nodosa (PAN), Crohn's

Surgery/trauma

- manipulation of sphincter of Oddi (e.g. ERCP), post-cardiac surgery, blunt trauma to abdomen, penetrating peptic ulcer

Hyperlipidemia (TG >11.3 mmol/L; >1000 mg/dL), hypercalcemia, hypothermia

Emboli or ischemia

Drugs/toxins

- azathioprine, mercaptopurine, furosemide, estrogens, methyl dopa, H₂-blockers, valproic acid, antibiotics, acetaminophen, salicylates, methanol, organophosphates, steroids (controversial)

Pathogenesis

- activation of proteolytic enzymes within pancreatic cells, starting with trypsin, leading to local and systemic inflammatory response
- in gallstone pancreatitis this is due to mechanical obstruction of the pancreatic duct by stones, in ethanol unknown
- in rare genetic diseases, which may be a model for ethanol, key problem is a mutation preventing the physiological trypsin breakdown required normally to stop proteolysis (e.g. mutant trypsin in hereditary pancreatitis; mutation in SPINK 1 gene which normally inhibits activated trypsin)

Pathology

- mild (interstitial)
 - peri-pancreatic fat necrosis
 - interstitial edema
- severe (necrotic)
 - extensive peri-pancreatic and intra-pancreatic fat necrosis
 - parenchymal necrosis and hemorrhage → infection in 60%
 - release of toxic factors into systemic circulation and peritoneal space (causes multi-organ failure)



Rule out other causes with specific treatment before making diagnosis of acute pancreatitis, which can only be treated by supportive means.

- severity of clinical features may not always correlate with pathology
- 3 phases:
 - local inflammation + necrosis → hypovolemia
 - systemic inflammation in multiple organs, especially in lungs, usually after IV fluids given → pulmonary edema
 - local complications 2 weeks after presentation → pancreatic sepsis/abscess

Signs and Symptoms

- pain: epigastric, noncolicky, constant, can radiate to back, may improve when leaning forward (Ingelfinger's sign)
- tender rigid abdomen; guarding
- nausea and vomiting
- abdominal distention from paralytic ileus
- fever: chemical, not due to infection
- jaundice: compression or obstruction of bile duct
- Cullen's/Grey-Turner's signs
- tetany: transient hypocalcemia
- hypovolemic shock: can lead to renal failure
- acute respiratory distress syndrome
- coma

Investigations

- increased serum pancreatic enzymes: amylase, lipase (more specific)
- ALT >100 strongly suggests biliary pancreatitis
- increased WBC, glucose; low calcium
- imaging: CT most useful for diagnosis and prognosis
 - x-ray: "sentinel loop" (dilated proximal jejunum), calcification and "colon cut-off sign" (colonic spasm)
 - U/S: best for evaluating biliary tree (67% sensitivity, 100% specificity)
 - CT scan with IV contrast: useful for diagnosis and prognosis because contrast seen only in viable pancreatic tissue, non-viable areas can be biopsied percutaneously to differentiate sterile from infected necrosis
 - ERCP or MRCP if cause uncertain, assess for duct stone, pancreatic or ampullary tumour, pancreas divisum

Prognosis

- usually a benign, self-limiting course, single or recurrent
- occasionally severe leading to:
 - shock
 - pulmonary edema
 - multi-organ dysfunction syndrome
 - GI ulceration due to stress
 - death
- mortality according to Ranson's criteria (see sidebar)
 - ≤2 criteria = <5% mortality
 - 3-4 criteria = 15-20%
 - 5-6 criteria = 40%
 - ≥7 criteria = >99%

Treatment

- goals:
 - (1) hemodynamic stability
 - (2) analgesia
 - (3) oxygen
 - (4) stop progression of damage – difficult
 - (5) treat local and systemic complications
- antibiotics controversial except in documented infection (use cephalosporins, imipenem)
- aspirate necrotic areas of pancreas to diagnose infection; drain if infected
- IV fluids (crystalloid or colloid)
 - beware third spacing of fluid, monitor urine output carefully
- NG suction (rests pancreas) if vomiting, stomach very dilated
- endoscopic sphincterotomy if gallstone pancreatitis
- nutritional support: nasoenteric jejunal feeding tube or TPN if cannot tolerate enteric feeds
 - recent evidence supports nasogastric enteral (or oral if feasible) feeds
- no benefit: glucagon, atropine, trasyolol, H₂-blockers, peritoneal lavage
- follow clinically and CT/ultrasound to exclude complications
- chief role of surgery is to drain fluid in the case of infected pancreatic necrosis (try to delay for >2 weeks to allow demarcation between viable and necrotic tissue)



Increased amylase

- Sensitive, not specific

Increased lipase

- Higher sensitivity and specificity
- Stays elevated longer



Ranson's Criteria: Prognostic Indicator of Mortality in Pancreatitis Not due to Gallstones (criteria slightly different for gallstone-induced pancreatitis)

At Admission

G: Blood Glucose >11 mmol/L (>200 mg/dL) (with no history of hyperglycemia)

A: Age >55

L: Serum LDH >350 IU/L

A: AST >250 IU/L

W: WBC >16 × 10⁹/L (16,000/mm³)

During First 48 hours

C: Serum Calcium <2 mmol/L (<8 mEq/L)

H: Hematocrit drop >10%

O: Arterial PO₂ <60 mmHg

B: Base deficit >4 mmol/L (>4 mEq/L)

B: BUN rise >1.8 mmol/L (>5 mg/dL)

S: Estimated fluid Sequestration >6 L

- Difficult course if 2 criteria present
- High mortality if ≥3 criteria present

Prophylactic Antibiotics Cannot Reduce Infected Pancreatic Necrosis and Mortality in Acute Necrotizing Pancreatitis: Evidence from a Meta-analysis of Randomized Controlled Trials

Am J Gastroenterol 2008; 103:104-10

Purpose: To review the effectiveness of IV antibiotics on pancreatic necrosis.

Study Selection: Randomized controlled trials comparing antibiotics with placebo or no treatment.

Results: Seven trials (n= 467) were included.

Antibiotics were not statistically superior to controls in reduction of infected necrosis and mortality.

Conclusion: Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in patients with acute necrotizing pancreatitis.

Note: In practice the temptation to give antibiotics for pancreatitis is mainly in the setting of a sick patient with fever and suggestive pancreatic necrosis on CT scan. It is difficult to determine whether pancreatic necrosis has become infected without aspiration biopsy. See *Curr Gastroenterol Rep* 2009; 11:104-10.

Late Complications

- pseudocysts – follow if asymptomatic, drain if symptomatic or growing
 - drain: choice of endoscopic, percutaneous under radiological guidance, or surgical
- infected necrosis/abscesses – antibiotics + percutaneous drainage, endoscopic vs. surgical
- bleeding – (1) gastric varices if splenic vein thrombosis; (2) pseudoaneurysm of vessels in areas of necrosis, especially splenic artery, (3) duodenal ulcer related to compression of duodenum by enlarged pancreas
- splenic and portal vein thrombosis – no effective therapy described, anticoagulation not proven, hazardous
- rare: diabetes, pancreatic duct damage

Chronic Pancreatitis

Definition

- irreversible damage to pancreas characterized by:
 - (1) pancreatic cell loss (from necrosis)
 - (2) inflammation
 - (3) fibrosis

Etiology/Pathophysiology

- alcohol (most common):
 - causes a larger proportion (>90%) of chronic pancreatitis than acute pancreatitis
 - changes composition of pancreatic juice (e.g. increases viscosity)
 - decreases pancreatic secretion of pancreatic stone protein (lithostathine) which normally solubilizes calcium salts
 - ♦ precipitation of calcium within pancreatic duct results in duct and gland destruction
 - toxic effect on acinar and duct cells – directly or via increasing free radicals
 - acinar cell injury leads to cytokine release, which stimulates pancreatic stellate cells to form collagen (leading to fibrosis)
 - varying degrees of ductular dilatation, strictures, protein plugs, calcification
 - no satisfactory theory to explain why only a minority of alcoholics develop pancreatitis
- unusual causes
 - cystic fibrosis
 - severe protein-calorie malnutrition
 - hereditary
 - idiopathic
- never gallstones – cause acute pancreatitis only

Signs and Symptoms

- early stages:
 - recurrent attacks of severe abdominal pain (upper abdomen and back)
 - chronic painless pancreatitis: 10%
- late stages: occurs in 15% of patients
 - malabsorption syndrome when >90% of function is lost, steatorrhea
 - diabetes, calcification, jaundice, weight loss, pseudocyst, ascites, GI bleed

Investigations

- laboratory:
 - increase in serum glucose
 - increase in serum ALP, less commonly bilirubin (jaundice)
 - serum amylase and lipase usually normal
- AXR: looking for pancreatic calcifications
- U/S: calcification, dilated pancreatic ducts, pseudocyst
- CT: calcification, dilated pancreatic ducts, pseudocyst
- MRCP or ERCP: abnormalities of pancreatic ducts-narrowing and dilatation
- 72-hour fecal fat test: exocrine function
- secretin test: gold standard, measures exocrine function but difficult to perform, unpleasant for patient, expensive
- fecal pancreatic enzyme measurement (elastase-1, chymotrypsin) available only in selected centres

Management

- most common problem is pain, difficult to control
- general management:
 - total abstinence from alcohol
 - enzyme replacement may help pain by resting pancreas via negative feedback
 - analgesics
 - celiac ganglion blocks
 - time – pain decreases with time as pancreas “burns out”



Symptoms of Chronic Pancreatitis

- Abdominal pain
- Diabetes
- Steatorrhea

Etiology = Almost Always Alcohol

Treatment

- Alcohol abstinence
- Pancreatic enzyme replacement
- Analgesics
- Pancreatic resection if ductular blockage

- endoscopy: sphincterotomy, stent if duct dilated, remove stones from pancreatic duct
- surgery: drain pancreatic duct (pancreaticojejunostomy) if duct dilated
 - resect pancreas if duct contracted
- steatorrhea:
 - pancreatic enzyme replacement
 - restrict fat, increase carbohydrate and protein (may also decrease pain)
 - neither endoscopy nor surgery can improve pancreatic function

Clinical Nutrition

Determination of Nutritional Status

- simple weight loss is most important parameter, expressed as body mass index (kg/m^2)

Investigations

- plasma proteins: albumin, pre-albumin (shorter half life than albumin), transferrin
 - decrease may indicate decreased nutritional status or disease state
- thyroid-binding globulin, retinol-binding protein (may be too sensitive)
- anthropometry (e.g. triceps skinfold thickness), grip strength less often used

Table 23. Areas of Absorption of Nutrients

	Fe	CHO	Proteins, Lipids Na, H ₂ O	Bile Acids	Vit B ₁₂
Duodenum	+++	+++	+++	+	
Jejunum		+	++	+	+
Ileum		+	++	+++	+++



Hypomagnesemia may be an initial sign of short bowel syndrome in patients who have undergone surgical bowel resection.



Most Common Indications for Artificial Nutrition Support include:

1. Preexisting nutritional deprivation
2. Anticipated or actual inadequate energy intake by mouth
3. Significant multiorgan system disease

Enteral Nutrition (EN)

Definition

- enteral nutrition (tube feeding) is a way of providing food through a tube placed in the stomach or the small intestine
- choice of tubes: nasogastric, nasojejunal, percutaneous endoscopic gastrostomy, percutaneous endoscopic jejunostomy or tubes can be placed radiologically, surgically

Indications

- oral feeding inadequate or contraindicated

Feeds

- polymeric feeds contain whole protein, carbohydrate, fat as a liquid, with or without fibre
- elemental feeds contain protein as amino acids, carbohydrate as simple sugars, fat content low (therefore high osmolality)
- specific diets: low carbohydrate/high fat solution for ventilated patients (carbohydrate has a high respiratory quotient so minimizes carbon dioxide production), high energy, low electrolyte solutions for dialysis patients

Relative Contraindications

- non-functioning gut (e.g. intestinal obstruction, enteroenteral or enterocutaneous fistulae)
- uncontrolled diarrhea
- GI bleeding

Complications

- aspiration
- diarrhea
- refeeding syndrome (rare): carbohydrate can stimulate excessive insulin release, leading to cellular uptake and low serum levels of phosphate, magnesium, potassium
- overfeeding syndrome (rare): hypertonic dehydration, hyperglycemia, hypercapnea, azotemia (from excess protein)

Enteral Nutrition Advantages over Parenteral Nutrition

- far fewer serious complications (especially sepsis)
- nutritional requirements for enterally administered nutrition better understood
- can supply gut-specific fuels such as glutamine and short chain fatty acids
- nutrients in the intestinal lumen prevent atrophy of the gut and pancreas
- prevents gallstones by stimulating gallbladder motility
- much less expensive

Parenteral Nutrition (PN)

Definition

- parenteral nutrition is the practice of feeding a person intravenously, bypassing the usual process of eating and digestion

Indications

- short term (<1 month)
 - whenever GI tract not functioning
 - only situations where PN has been well shown to increase survival are after bone marrow transplant and in short bowel syndrome, some evidence for benefit in gastric cancer
 - preoperative: only useful in severely malnourished (e.g. loss of >15% of pre-morbid weight, serum albumin <28 g/l or <2.8 g/dl), and only if given for ≥2 weeks
 - renal failure: PN shown to increase rate of recovery; no increase in survival
 - liver disease: branched chain amino acids may shorten duration of encephalopathy; no increase in survival
 - IBD: PN closes fistulae and heals acute exacerbations of mucosal inflammation, but effect is transient (EN is equally effective)
 - some evidence for efficacy, but convincing data not available for:
 - radiation/chemotherapy-induced enteritis
 - AIDS with wasting diarrhea
 - severe acute pancreatitis
- long term (>1 month): can be given at home
 - severe untreatable small bowel disease (e.g. radiation enteritis, extensive Crohn's disease, high output fistulae)
 - following surgical resection of >70% of bowel (e.g. bowel infarction)
 - severe motility diseases (e.g. scleroderma affecting bowel)

Relative Contraindications

- functional GI tract for enteral nutrition
- active infection; at least until appropriate antibiotic coverage
- inadequate venous access; triple-lumen central venous lines usually prevent this problem
- unreliable patient or clinical setting

Complications of PN

- sepsis: most serious of the common complications
- mechanical pneumothorax from insertion of central line, catheter migration and thrombosis, air embolus
- metabolic: CHF, hyperglycemia, gallstones, cholestasis

Visualizing the GI Tract

- see also [Diagnostic Medical Imaging](#), D11

Esophagus, Stomach, Duodenum

- endoscopy (esophagogastroduodenoscopy) – best visualization of mucosa, allows for therapeutic intervention (band varices, cauterize/clip/inject bleeding ulcers)
 - consider barium swallow first if dysphagia, decreased level of consciousness (increases risk of aspiration), inability to cooperate (increases risk of pharyngeal trauma during intubation)
 - endotracheal intubation first if massive upper GI bleed, acidosis, unable to protect airway

Small Bowel

- most difficult to visualize if mucosal detail is needed
- most accurate is wireless endoscopy capsule (26 x 11 mm capsule is swallowed, transmits images to a computer; contraindicated if bowel obstruction)
- CT enterography (use enteroclysis if suspect obstruction) more accurate than small bowel swallow, but both have low sensitivity
- MRI enteroclysis increasingly available
- “double balloon” endoscopy (endoscope with balloons proximally and distally to propel endoscope into jejunum from mouth or into ileum from anus) may be most sensitive but currently available only in selected centres; technically demanding

Colon and Terminal Ileum

- colonoscopy, with biopsy if required; contraindicated in acute diverticulitis, severe colitis (increased risk of perforation)
- CT colonoscopy (“virtual colonoscopy”) more accurate in diagnosing diverticulosis, extrinsic pressure on colon (e.g. ovarian cancer compressing sigmoid colon), fistulae



Whenever possible, enteral nutrition is ALWAYS preferable over PN!

Pancreatic/Biliary Duct

- MRCP (magnetic resonance cholangiopancreatography = MRI of pancreas/bile duct) almost as sensitive as ERCP (endoscopic retrograde cholangiopancreatography) to determine if bile duct obstruction present, but less accurate in determining cause of obstruction (tumour, stone, stricture)
- use ERCP if endoscopic draining likely to be necessary, strong suspicion of stone or ampullary tumour
- MRCP reported to have lower sensitivity in sclerosing cholangitis than ERCP

Common Medications

Table 24. Common Drugs Prescribed in Gastroenterology

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
Proton Pump Inhibitors (H ⁺ /K ⁺ -ATPase inhibitors)	omeprazole	Losec®/Prilosec®	20 mg OD	Inhibits gastric enzymes H ⁺ /K ⁺ -ATPase (proton pump)	Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, reflux esophagitis, symptomatic GERD, dyspepsia, Zollinger-Ellison syndrome, eradication of <i>H. pylori</i> (combined with antibiotics)	Hypersensitivity to drug	Dizziness, headache, flatulence, abdo pain, nausea, rash, increased risk of osteoporotic fracture (secondary to impaired calcium absorption)
	lansoprazole	Prevacid®	Oral therapy: 15-30 mg OD (before breakfast) IV therapy: 30 mg OD	Same as above	Same as above	Same as above	Same as above
	pantoprazole	Pantoloc® Protonix®	40 mg OD for UGIB: 80 mg bolus then 8 mg/h infusion	Same as above	Same as above and UGIB	Same as above	Same as above
	rabeprazole	Pariet®/Aciphex®	40 mg OD	Same as above	Same as above	Same as above	Same as above
	esomeprazole	Nexium®	20-40 mg OD	Same as above	Same as above	Same as above	Same as above
Histamine H₂-receptor Antagonists	ranitidine	Zantac®	300 mg OD or 150 mg bid IV therapy: 50 mg q8h (but tachyphylaxis a problem)	Inhibits gastric histamine H ₂ -receptors	Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, ulcer prophylaxis, reflux esophagitis, symptomatic GERD, Zollinger-Ellison syndrome	Hypersensitivity to drug	Confusion, dizziness, headache, arrhythmias, constipation, nausea, agranulocytosis, pancytopenia, depression
	famotidine	Pepcid®	Oral therapy: duodenal/gastric ulcers: 40 mg qhs GERD: 20 mg bid IV therapy: 20 mg bid	Same as above	Same as above	Same as above	Same as above
Stool Softener	docusate sodium	Colace®	100-400 mg daily, divided in 1-4 doses	Promotes incorporation of water into stool	Relief of constipation	Presence of abdo pain, fever, nausea and vomiting	Throat irritation, abdo cramps, rashes
Laxative	lactulose	Lactulose/ Constulose®	Constipation: 15-30 ml OD to bid Encephalopathy: 15-30 ml bid to qid	Poorly absorbed in GI tract and is broken down by colonic bacteria into lactic acid into colon, increased osmotic colonic contents, increases stool volume	Chronic constipation, prevention and treatment of portal-systemic encephalopathy	Patients who require a low galactose diet	Flatulence, intestinal cramps, nausea, diarrhea if excessive dosage

Table 24. Common Drugs Prescribed in Gastroenterology (continued)

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
Peristaltic Stimulant	senna	Senokot®	Tablets: 1-4 qhs Syrup: 10-15 ml qhs	Senna glycosides are converted into aglycones in the colon and function as laxative agents by altering colonic water and electrolyte transport	Relief of constipation	Patients with acute abdomen	Abdo cramps, discolouration of breast milk, urine, feces, melanosis coli and atonic colon from prolonged use (controversial)
Antidiarrheal Agents	loperamide	Imodium®	Acute diarrhea: 4 mg initially, followed by 2 mg after each unformed stool	Acts as antidiarrheal via cholinergic, oncholingeric, opiate and nonopiate receptor-mediated mechanisms; decreases activity of myenteric plexus	Adjunctive therapy for acute non-specific diarrhea, chronic diarrhea associated with IBD and for reducing the volume of discharge for ileostomies, colostomies and other intestinal resections	Children <2 yrs, known hypersensitivity to drug, acute dysentery characterized by blood in stools and fever, acute ulcerative colitis or pseudomembranous colitis associated with broad-spectrum antibiotics	Abdo pain or discomfort, drowsiness or dizziness, tiredness, dry mouth, nausea and vomiting, hypersensitivity reaction
	diphenoxylate/atropine	Lomotil®	5 mg tid to qid	Inhibits GI propulsion via direct action on smooth muscle, resulting in a decrease in peristaltic action and increase in transit time	Adjunctive therapy for diarrhea, as above	Hypersensitivity to diphenoxylate or atropine, jaundice, pseudomembranous enterocolitis, diarrhea caused by enterotoxin producing bacteria	Dizziness, drowsiness, insomnia, headache, nausea, vomiting, cramps, allergic reaction
IBD Agents	mesalamine	Pentasa® Salofalk® Asacol® Mesasal®	CD: 1g tid/qid Active UC: 1g qid Maintenance UC: 1.6 g divided doses daily also as suppositories and enemas	5-ASA: Blocks arachidonic acid metabolism to prostaglandins and leukotrienes	IBD	Hypersensitivity to mesalamine salicylates	Abdo pain, constipation, arthralgia, headache
	sulfasalazine	Salazopyrin®	3-4 g/d in divided doses	Compound composed of 5-ASA bound to sulfapyridine, hydrolysis by intestinal bacteria releases 5-ASA, the active component	Colonic disease	Hypersensitivity to sulfasalazine, sulfa drugs, salicylates; intestinal or urinary obstruction, porphyria	Rash, loss of appetite, nausea, vomiting, headache, oligospermia (reversible)
	prednisone		20-40 mg OD for acute exacerbation	Anti-inflammatory	Mod-severe CD and UC		Complications of steroid therapy
Immuno-suppressive Agents	6-mercaptopurine (6-MP)	Purinethol®	CD: 1.5 mg/kg/day	Immunosuppressive	IBD: active inflammation and to maintain remission	Hypersensitivity to mercaptopurine, prior resistance to mercaptopurine or thioguanine, history of treatment with alkylating agents, hypersensitivity to azathioprine, pregnancy	Pancreatitis, bone marrow suppression, increased risk of cancer
	azathioprine	Azasan® Imuran®	IBD: 2-3 mg/kg/day	Same as above	Same as above	Same as above	Same as above
Immunomodulators	infliximab	Remicade®	5-10 mg/kg IV over 2 h	Antibody to tumour necrosis factor	Medically refractory CD	Heart failure, moderate to severe, doses >5 mg/kg	Reported cases of reactivated TB, PCP, lymphoma, other infections

References

Atlas

Kandel, G., Division of Gastroenterology, SMH.

Olscamp, G., Division of Gastroenterology.

Saibil, F., Division of Gastroenterology, SWCHSC.

Haber, G., Division of Gastroenterology, Lennox Hall Hospital, New York.

Esophageal and Gastric Disease

Devault, K.R., Castell, D.O.: Guidelines for the diagnoses and treatment of gastroesophageal reflux disease. *Arch Intern Med.* 115:2165-2173, 1995.

DiPalma JA. Management of severe gastroesophageal reflux disease. *Journal of Clinical Gastroenterology.* 32(1): 19–26, 2001.

Wilcox, C.M., Karowe, M.W.: Esophageal infections: etiology, diagnosis, and management. *Gastroenterology.* 2:188, 1994.

Stomach and Duodenum

American Gastroenterological Association Position statement: Evaluation of dyspepsia. *Gastroenterology.* 114:579-581, 1998.

Howden, C.W., Hunt, R.H.: Guidelines for the management of *Helicobacter Pylori* infection. *Am J Gastroenterology.* 93:2330-2338, 1998.

Hunt RH, Fallone CA, Thomson ABR. Canadian *Helicobacter pylori* consensus conference update: infection in adults. *J. Gastroenterol.* 13: 213-6, 1999.

Laine, L., Peterson W.L.: Bleeding peptic ulcer. *NEJM.* 331:717-727, 1994.

Lanza, F.L.: A guideline for the treatment and prevention of NSAID-induced ulcer. *Am J Gastroenterology.* 93:2037-2046, 1998.

McColl, K.E. Clinical Practice *Helicobacter pylori* infection. *MEJM.* 362(17): 1597-601, 2010.

Peek, R.M., Blaser M.J.: Pathophysiology of *Helicobacter Pylori*-induced gastritis and peptic ulcer disease. *Am J Med.* 102:200-207, 1997.

Salcedo JA, Al-Kawas F (1998). Treatment of *Helicobacter pylori* infection. *Arch Intern Med.* 158: 842-51, 1998.

Schmid CH, Whiting G, Cory D et al. Omeprazole plus antibiotics in the eradication of *Helicobacter pylori* infection: a meta-regression analysis of randomized controlled trials. *Am J Ther.* 6(1): 25-36, 1999.

Soll AH. Practice Parameters: committee of the American College of Gastroenterology: Medical treatment of peptic ulcer disease. I. 275: 622, 1996.

Thijs JC, van Zwet AA, Thijs WJ, et al. Diagnostic tests for *Helicobacter pylori*: A prospective evaluation of their accuracy, without selecting a single test as the gold standard. *Am J Gastroenterology.* 91(10): 2125-29, 1996.

Small and Large Bowel

Aranda-Michel, J., Giannella, R. Acute Diarrhea: A Practical Review. *American Journal of Medicine.* 10(6): 670-676, 1999.

Colorectal cancer screening: Recommendation statement from the Canadian Task Force on Preventative Health Care. *CMAJ.* 165(2): 206-8, 2001.

Donowitz M., Kokke FT., Saidi R. Evaluation of Patients with Chronic Diarrhea. *NEJM.* 332 (11): 725:729, 1995.

Drossman DA. The Functional Gastrointestinal disorders and the Rome III process. *Gastroenterology.* 130:1377-1390, 2006.

Forrest JA, Finlayson ND, Shearman DJ. Endoscopy in Gastrointestinal Bleeding. *Lancet.* 1974(17):394-397.

Ghosh, S., Shand A. Ulcerative Colitis. *BMJ.* 320 (7242) 1119-1123, 2000.

Hanauer SB. Drug therapy: Inflammatory Bowel Disease. *NEJM.* 334(13): 841-848, 1996.

Horwitz, B.J., Fisher RS. Current Concepts: The Irritable Bowel Syndrome. *NEJM.* 344(24): 1846-1850, 2001.

Jennings, JSR., Howdle, PD. Celiac Disease. *Current Opinion in Gastroenterology.* 17(2): 118:126, 2001.

Liver and Biliary Tract

Angulo P. Primary biliary cirrhosis and primary sclerosing cholangitis. *Clinics in Liver Disease.* 3(3): 529-70, 1999.

Bockus Gastroenterology. Volume 4Haubrich, W.S., Schaffner, F, Berk, J.E. 5th Edition W.B. Saunders Company. Chapter 74. Pregnancy-Related Hepatic and Gastrointestinal Disorders. Pages: 1448-1458

Cecil Essentials of Medicine. 5th edition. Andreoli, T, Carpenter, C., Griggs, R. and Loscalzo, J. eds. W.B. Saunders Company, Philadelphia, 2001.

Custis K. Common biliary tract disorders. *Clin Fam Pract.* 2(1): 141-154, 2000.

Diehl AM. Alcoholic liver disease. *Clinics in Liver Disease.* 2(1): 103-118, 1998.

Gastrointestinal and Liver Disease. Pathophysiology/Diagnosis/Management. Volume 2 Feldman, M., Friedman, L.S. and Sleisenger, M.H. 7th Edition Malik AH. Acute and chronic viral hepatitis. *Clin Fam Pract.* 2(1): 35-57, 2000.

Reynolds, T. Ascites. *Clinics in Liver Disease.* 4(1): 151-168, 2000.

Sandowski SA. Cirrhosis. *Clin Fam Pract.* 2(1): 59-77, Mar 2000.

Saunders. Chapter 184: Pregnancy and the Gastrointestinal Tract. Pages 3446-3452.

Sherman, M. Chronic viral hepatitis and chronic liver disease. *The Canadian Journal of Diagnosis.* 18(6):81-90, 2001.

Sternlieb I. Wilson's disease. *Clinics in Liver Disease.* 4(1): 229-239, 2000.

Williams, Simmel. Does this patient have ascites? *JAMA.* 287(19), 1992.

Yapp TR. Hemochromatosis. *Clinics in Liver Disease.* 4(1): 211-228, 2000.

Yu AS. Management of ascites. *Clinics in Liver Disease.* 5(2): 541, 2001.

Pancreas

Beckinham IJ, Borman PC. Acute Pancreatitis. *BMJ.* 322: 595-598. 2001

Beckinham IJ, Borman PC. Chronic Pancreatitis. *BMJ.* 322: 595-598. 2001

Steer, M.L. Chronic pancreatitis. *NEJM.* 332:1482-1490, 1995.

Sternby B et al. What is the best biochemical test to diagnose acute pancreatitis? A prospective clinical study. *Mayo Clin Proc.* 71: 1138, 1996.

Whytcomb DC. Acute pancreatitis. *NEJM.* 2142-2150, 2006.

Rational Clinical Examination

Grover SA, Barkun AN, Sackett DL. Does this patient have splenomegaly? *JAMA.* 270(18): 2218-21, 1993.

Kitchens JM. Does this patient have an alcohol problem? *JAMA.* 272(22): 1782-1787, 1994.

Naylor CD. Physical exam of the liver. *JAMA.* 271 (23): 1859:1865, 1994.

Williams JW, Simel DL. Does this patient have ascites? How to divine fluid in the abdomen. *JAMA.* 267 (19): 2645-48, 1992.

Notes

Lined area for notes.

Annie Doan, Peter Szasz and Nathalie Wong-Chong, chapter editors
 Alaina Garbens and Modupe Oyewumi, associate editors
 Adam Gladwish, EBM editor
 Dr. Tulin Cil and Dr. David Urbach, staff editors

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Basic Anatomy Review

Common Acronyms

AAA – abdominal aortic aneurysm
 ABG – arterial blood gas
 ABI – ankle brachial index
 APR – abdominal perineal resection
 BRBPR – bright red blood per rectum
 CBD – common bile duct
 CVA – costovertebral angle
 CVP – central venous pressure
 DPL – diagnostic peritoneal lavage
 EBL – estimated blood loss
 OGD/EGD – esophagogastro-duodenoscopy
 ERCP – endoscopic retrograde cholangiopancreatography
 EUA – examination under anesthesia
 FAST – focused abdominal sonogram for trauma
 FNA – fine needle aspiration
 FOBT – fecal occult blood test
 I&D – incision and drainage
 LBO – large bowel obstruction
 LES – lower esophageal sphincter
 LGIB – lower GI bleed
 MAE – moving all extremities
 MEN – multiple endocrine neoplasia
 MIS – minimally invasive surgery
 MRCP – magnetic resonance cholangiopancreatography
 NGT – nasogastric tube
 POD – postoperative day
 SBO – small bowel obstruction
 SIADH – syndrome of inappropriate anti-diuretic hormone
 TEE – transesophageal echocardiogram
 TTE – transthoracic echocardiogram
 UGIB – upper GI bleed

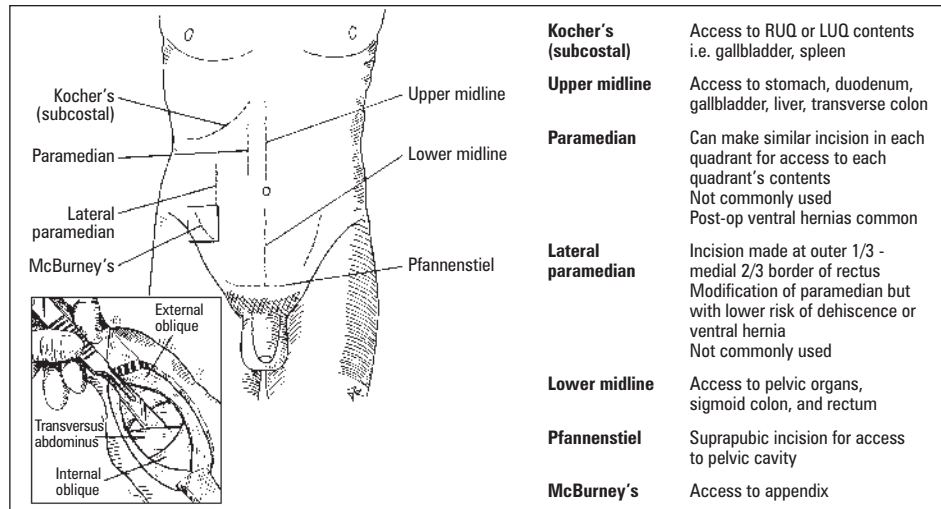


Figure 1. Abdominal Incisions

Layers from Superficial to Deep

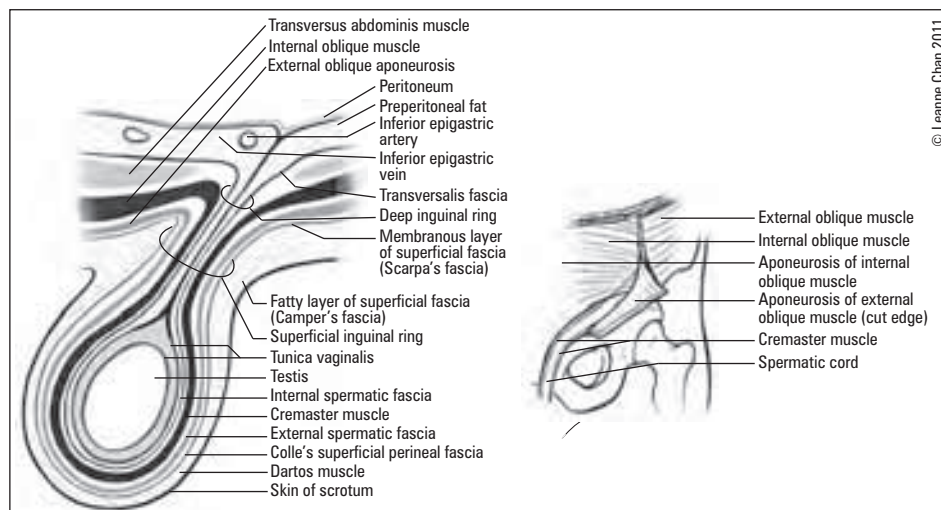


Figure 2. Continuity of the Abdominal Wall with Layers of the Scrotum and Spermatic Cord

- skin (epidermis, dermis, subcutaneous fat)
- superficial fascia
 - Camper's fascia (fatty) → Dartos
 - Scarpa's fascia (membranous) → Colle's superficial perineal fascia
- muscle (see Figure 2 and Figure 3)
 - external oblique → inguinal ligament → external spermatic fascia → fascia lata
 - internal oblique → cremasteric muscle/fascia
 - transversus abdominus → posterior inguinal wall
- transversalis fascia → internal spermatic fascia
- preperitoneal fat
- peritoneum → tunica vaginalis
- at midline
 - rectus abdominus muscle: in rectus sheath, divided by linea alba
- above arcuate line (semicircular line of Douglas), which is midway between symphysis pubis and umbilicus
 - anterior rectus sheath = external oblique aponeurosis and anterior leaf of internal oblique aponeurosis
 - posterior rectus sheath = posterior leaf of internal oblique aponeurosis and transversus muscle aponeurosis
- below arcuate line
 - anterior rectus sheath = aponeurosis of external, internal oblique, transversus muscles
 - posterior rectus sheath = transversalis fascia
- arteries: superior epigastric (branch of internal thoracic), inferior epigastric (branch of external iliac); both arteries anastomose and lie behind the rectus muscle

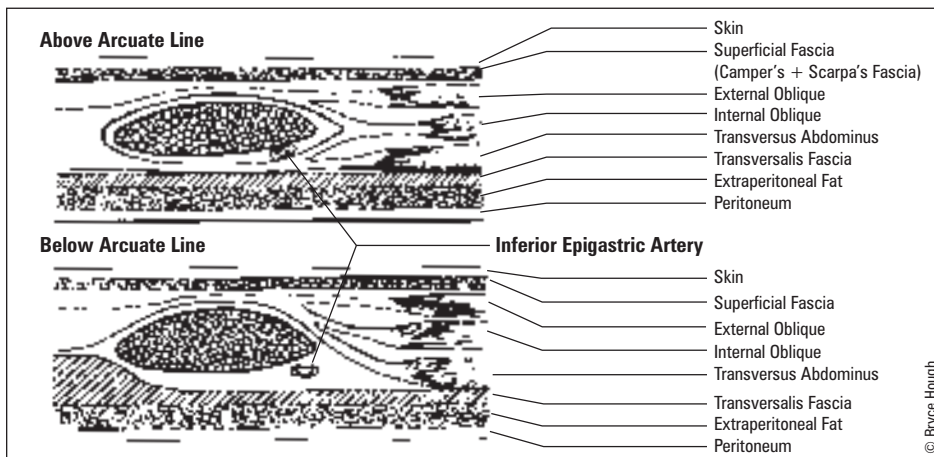


Figure 3. Midline Cross-Section of Abdominal Wall

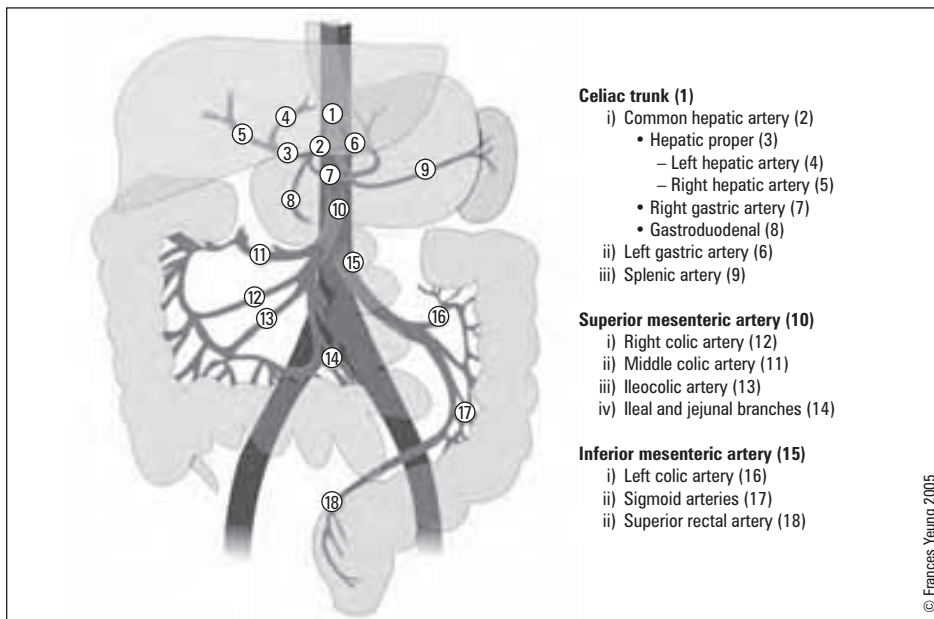


Figure 4. Blood Supply to the GI Tract

Venous Flow

- end point is the portal vein

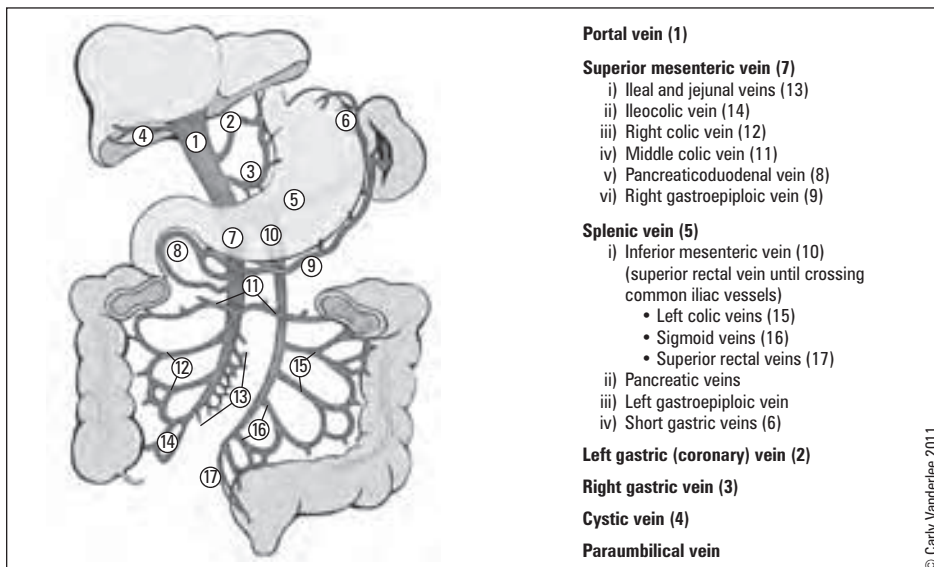


Figure 5. Venous Drainage of the GI Tract

Organ	Arteries
Liver	Left and right hepatic (branches of hepatic proper)
Spleen	Splenic
Gallbladder	Cystic (Off right hepatic artery)
Stomach	1. Lesser curve-right and left gastric 2. Greater curve-right (off gastroduodenal) and left gastroepiploic (off splenic artery) (gastro-omental) 3. Fundus-short gastrics (off splenic)
Duodenum	1. Gastroduodenal 2. Pancreaticoduodenals (off superior mesenteric)
Pancreas	1. Splenic branches 2. Pancreaticoduodenals
Small intestine	1. Superior mesenteric branches – jejunal, ileal, ileocolic
Large intestine	1. Superior mesenteric branches – right colic, middle colic 2. Inferior mesenteric branches – left colic, sigmoid, rectal

Differential Diagnoses of Common Presentations

Acute Abdominal Pain

Table 1. Differential Diagnosis of Acute Abdominal Pain

RUQ	EPIGASTRIC	LUQ
Hepatobiliary Biliary colic Cholecystitis Cholangitis CBD obstruction (stone, tumour) Hepatitis Budd-Chiari Hepatic abscess/mass Right subphrenic abscess Gastrointestinal Pancreatitis Presentation of gastric, duodenal or pancreatic pathology Hepatic flexure pathology (CRC, subcostal incisional hernia) Genitourinary Nephrolithiasis Pyelonephritis Renal: mass, ischemia, trauma Cardiopulmonary RLL Pneumonia Effusion/Empyema CHF (causing hepatic congestion and R pleural effusion) MI Pericarditis Pleuritis Miscellaneous Herpes zoster Trauma Costochondritis	Cardiac Aortic dissection/ruptured AAA MI Pericarditis Gastrointestinal Gastritis GERD/Esoophagitis Peptic ulcer disease Pancreatitis Mallory-Weiss tear DIFFUSE Gastrointestinal Peritonitis Early appendicitis, perforated appendicitis Mesenteric ischemia Gastroenteritis/Colitis Constipation Bowel obstruction Pancreatitis Inflammatory bowel disease Irritable bowel syndrome Ogilvie's syndrome Cardiovascular/Hematological Aortic dissection/ruptured AAA Sickle cell crisis Genitourinary/Gynecological Perforated ectopic pregnancy PID Acute urinary retention Endocrinological Carcinoid syndrome Diabetic ketoacidosis Addisonian crisis Hypercalcemia Other Lead poisoning Tertiary syphilis	Pancreatic Pancreatitis (acute vs. chronic) Pancreatic pseudocyst Pancreatic tumours Gastrointestinal Gastritis Peptic ulcer disease Splenic flexure pathology (e.g. CRC, ischemia) Splenic Splenic infarct/abscess Splenomegaly Splenic rupture Splenic aneurysm Cardiopulmonary (see RUQ and Epigastric) Genitourinary (see RUQ) LLQ Gastrointestinal Diverticulitis Diverticulosis Colon/Sigmoid/Rectal Cancer Fecal impaction Proctitis (ulcerative colitis, infectious; i.e. gonococcus or chlamydia) Sigmoid volvulus Hernia See gynecological, urological, and extraperitoneal as per RLQ and suprapubic
RLQ Gastrointestinal Appendicitis Crohn's disease Tuberculosis of the ileocecal junction Cecal tumour Intussusception Mesenteric lymphadenitis (Yersinia) Cecal diverticulitis Cecal volvulus Hernia: amyands, femoral, inguinal obstruction (and resulting cecal distention) Gynecological See 'suprapubic' Genitourinary See 'suprapubic' Extraperitoneal Abdominal wall hematoma/abscess Psoas Abscess	SUPRAPUBIC Gastrointestinal (see RLQ/ LLQ) Acute appendicitis IBD Gynecological PID Ectopic pregnancy Endometriosis Threatened/Incomplete abortion Hydrosalpinx/Salpingitis Ovarian torsion Hemorrhagic fibroid Tubo-ovarian abscess Gynecological tumours Genitourinary Cystitis (infectious, hemorrhagic) Hydroureter/Urinary Colic Epididymitis Testicular torsion Acute urinary retention Extraperitoneal Rectus sheath hematoma	



In all patients presenting with an acute abdomen, order the following:

1. Amylase/lipase
2. Urinalysis
3. Beta-hCG (in women)
4. Consider CXR + troponins

This will help rule out "non-GI surgical" causes!



Pancreatitis can look like a surgical abdomen, but is rarely an indication for laparotomy.



Referred Pain

Biliary colic: to right shoulder or scapula
 Renal colic: to groin
 Appendicitis: periumbilical to right lower quadrant (RLQ)
 Pancreatitis: to back
 Ruptured aortic aneurysm: to back or flank
 Perforated ulcer: to RLQ (right paracolic gutter)
 Hip pain: to groin

Abdominal Mass

Table 2. Differential Diagnosis of Abdominal Mass

Right Upper Quadrant (RUQ)	Upper Midline	Left Upper Quadrant (LUQ)
Gallbladder – cholecystitis, cholangiocarcinoma, cholelithiasis	Pancreas – pancreatic adenocarcinoma, IPMT, other pancreatic cancer, pseudocyst	Spleen – splenomegaly, tumour, abscess, subcapsular splenic hemorrhage, can also present as RLQ mass if extreme splenomegaly
Biliary tract – Klatskin tumour	Abdominal aorta – AAA (pulsatile)	Stomach – tumour
Liver – hepatomegaly, hepatitis, abscess, tumour (hepatocellular carcinoma, metastatic tumour, etc.)	Gastric tumour (adenocarcinoma, gastrointestinal stromal tumour, carcinoid tumour), MALT lymphoma	
Right Lower Quadrant (RLQ)	Lower Midline	Left Lower Quadrant (LLQ)
Intestine – stool, tumour (CRC), mesenteric adenitis, appendicitis, appendicular phlegmon or other abscess, typhlitis, intussusception, Crohn's inflammation	Uterus – pregnancy, leiomyoma (fibroid), uterine cancer, pyometria, hematometria	Intestine – stool, tumour, abscess (see RLQ)
Ovary – ectopic pregnancy, cyst (physiological vs. pathological), tumour (serous, mucinous, struma ovarii, germ cell, krukberg)	GU – bladder distention, tumour	Ovary – ectopic pregnancy, cyst, tumour (see RLQ)
Fallopian tube – ectopic pregnancy, tubo-ovarian abscess, hydrosalpinx, tumour		Fallopian tube – ectopic pregnancy, tubo-ovarian abscess, hydrosalpinx, tumour



Indications for Urgent Operation

IHOP
Ischemia
Hemorrhage
Obstruction
Perforation

GI Bleeding

- see Gastroenterology, G26-29

Indications for Surgery

- failure of medical management
- prolonged bleeding, significant blood loss (requiring >6 units of pRBCs in a short period of time), high rate of bleeding, hypotension
- bleeding that persists despite endoscopic and angiographic therapeutic maneuvers

Surgical Management of GI Bleeding

- upper GI bleeding:
 - bleeding from a source proximal to the ligament of Treitz
 - often presents with hematemesis and melena unless very brisk (then can present with BRBPR, hypotension, tachycardia)
 - initial management with endoscopy; if fails, then consider surgery
- lower GI bleeding:
 - bleeding from a source distal to the ligament of Treitz
 - often presents with BRBPR unless proximal to transverse colon
 - ♦ may occasionally present with melena
 - initial management with colonoscopy to detect and potentially stop source of bleeding
 - angiography, RBC scan to determine source as indicated
 - ♦ surgical intervention if no source found

Table 3. Differential Diagnosis of GI Bleeding

Anatomical Source	Etiology	
Hematological	Excess anticoagulation (coumadin, heparin, etc.)	DIC Congenital bleeding disorders
Nose	Epistaxis	
Esophagus	Esophageal varices Mallory-Weiss tear Esophagitis	Aorto-esophageal fistula (generally post endovascular aortic repair)* Esophageal cancer
Stomach	Gastritis Gastric varices Dieulafoy lesion	Gastric ulcer Gastric cancer*
Duodenum	Duodenal ulcer Perforated duodenal ulcer*	Duodenal cancer*
Jejunum	Tumours*	
Ileum and Ileocecal Junction	Meckel's diverticulum (rare surgical management) Small bowel obstruction	Crohn's disease* Tuberculosis of ileocecal junction

Table 3. Differential Diagnosis of GI Bleeding (continued)

Anatomical Source	Etiology	
Large Intestine	Colorectal cancer* Mesenteric thrombosis/ischemic bowel* Ulcerative colitis* (subtotal colectomy if failure of medical management) Angiodysplasia	Crohn's disease (less frequently presents with bleeding)* Pancolitis (infectious, chemotherapy or radiation induced) Bleeding post-gastrointestinal anastomosis
Sigmoid	Diverticulosis* Sigmoid cancer* Bleeding post-polypectomy	Polyps* (surgical management if not amenable to colonoscopic polypectomy) Inflammatory bowel disease (IBD)
Rectum and Anus	Hemorrhoids Fissures Rectal cancer* Anal varices	Polyps* (surgical management if not amenable to polypectomy) Crohn's or ulcerative colitis* Solitary rectal ulcer syndrome

*Managed surgically in most cases



Jaundice

- see Gastroenterology, G44

Differential Diagnosis

- **pre-hepatic**
 - pathology occurring prior to the liver
 - ♦ hemolysis
 - ♦ Gilbert's disease, Crigler-Najjar disease
- **hepatic**
 - pathology occurring at the level of the liver
 - ♦ viral hepatitis
 - ♦ alcoholic hepatitis, cirrhosis
 - ♦ drug-induced hepatitis – acetaminophen, erythromycin, isoniazid, valproic acid, phenytoin, oral contraceptive pill
 - ♦ Dubin-Johnson syndrome
- **post-hepatic:**
 - pathology is located after the conjugation of bilirubin in the liver
 - ♦ choledocholithiasis, cholangitis, sclerosing cholangitis, choledochal cyst
 - ♦ benign biliary stricture
 - ♦ carcinoma – bile duct, head of pancreas, ampulla of Vater, duodenum



Bilirubin Levels

	Prehepatic	Intrahepatic	Posthepatic
Serum bilirubin			
Indirect	↑	↑	N
Direct	N	↑	↑
Urine			
Urobilinogen	↑	↑	Absent
Bilirubin	–	+	+
Fecal			
Urobilinogen	↑	↑	Absent



Approach to the Critically Ill Surgical/Trauma Patient ABC, I'M FINE ABC

- I** – IV: 2 large bore IV's with NS, wide open
- M** – Monitors: O₂ sat, ECG, BP
- F** – Foley catheter to measure urine output
- I** – Investigations: bloodwork
- N** – NG tube if indicated
- E** – "Ex" rays (abdomen 3 views, CXR), other imaging



Pre and Post-Op Orders

Admit to ward X under Dr. Y
Diagnosis
Diet
Activity
Vitals
IV, Investigations, Ins & Outs
Drugs, Dressings, Drains
Special procedures



DRUGS – 6 A's

Analgesia
Anti-emetic
Anti-coagulation
Antibiotics
Anxiolytics
All other patient meds

Preoperative Preparations

Considerations

- informed consent (see Ethical, Legal and Organizational Aspects of Medicine, ELOAM8)
- consults – anesthesia, medicine, cardiology as indicated
- NPO after midnight, AAT (activity as tolerated), VSR (vital signs routine)
- IV – balanced crystalloid at maintenance rate (4:2:1 rule → roughly 100-125 cc/hr): normal saline or Ringer's lactate; bolus to catch up on estimated losses from bowel prep
- patient's regular meds including prednisone – consider pre-op stress dose if prednisone used in past year
- prophylactic antibiotics (within 1 hour prior to incision): usually cefazolin (Ancef®) ± metronidazole (Flagyl®)
- bowel prep: cleans out bowel and decreases bacterial population
 - oral cathartic (e.g. fleet Phosphosoda®) starting previous day
 - used for left-sided or rectal resections (routine use is controversial and probably unnecessary)
- consider DVT prophylaxis for all inpatient surgery (heparin)
- hold ASA x 1 week preop
- smoking cessation x 6 weeks preop can significantly decrease postop complications

Investigations

- blood components: group and screen or cross and type depending on procedure
- CBC, electrolytes, BUN, creatinine
- INR/PT, PTT with history of bleeding disorder
- ABGs if predisposed to respiratory insufficiency
- CXR (PA and lateral) if >50 years old or previously abnormal within past 6 months
- ECG if >50 years old or as indicated by history

Drains

- nasogastric (NG) tube:
 - indications: gastric decompression, analysis of gastric contents, irrigation/dilution of gastric contents, feeding (only if necessary due to risk of aspiration → naso-jejunal tube preferable)
 - contraindications: suspected basal skull fracture, obstruction of nasal passages due to trauma
- Foley catheter:
 - indications: to accurately monitor urine output, decompression of bladder, relieve obstruction
 - contraindications: suspected urethral injury, difficult insertion of catheter

Surgical Complications



Postoperative Fever

- fever does not necessarily imply infection
- timing of fever may help identify cause
- POD #0-2:
 - atelectasis (most common cause of fever on POD #1)
 - early wound infection (especially *Clostridium*, Group A *Streptococcus* – feel for crepitus and look for “dishwater” drainage)
 - aspiration pneumonitis
 - other: Addisonian crisis, thyroid storm, transfusion reaction
- POD #3:
 - infections more likely
 - UTI, wound infection, IV site infection, septic thrombophlebitis
- POD #5+:
 - leakage at bowel anastomosis (tachycardia, hypotension, oliguria, abdominal pain)
 - intra-abdominal abscess (usually POD #5-10)
 - DVT/PE (can be anytime post-op, most commonly POD #7-10)
 - drug fever (POD #6-10)
- other: cholecystitis, peri-rectal abscess, URTI, infected seroma/biloma/hematoma, parotitis, *C. difficile* colitis, endocarditis



“5 W’s” of Post-Op Fever

Wind (pulmonary)

Water (urine-UTI)

Wound

Walk (DVT/PE)

Wonder drugs (drug fever)

Correlate with time spent in post-op period.

Treatment

- treat primary cause
- antipyrexia (e.g. acetaminophen)

Wound Complications

WOUND CARE

- epithelialization of wound occurs 48 hours after closure
- dressings applied in the operating room can be removed POD #2-4
- leave uncovered if wound is dry
- remove dressings if wet, signs of infection (fever, tachycardia, pain)
- examination of the wound: inspect, compress adjacent areas, swab drainage for C&S and Gram stain
- skin sutures and staples can be removed POD #5:
 - exceptions: incision crosses crease (groin), closed under tension, in extremities (hand) or patient factors (elderly, corticosteroid use) removed POD #14, earlier if signs of infection
- can bathe POD #2-3
- negative pressure dressings consist of gel foam and suction, promote granulation
 - ideal for large (grafted sites) or nonhealing wounds (irradiated skin, ulcer)

DRAINS

- placed intra-operatively to prevent fluid accumulation (blood, pus, serum, bile, urine)
- potential route of infection, bring out through separate incision (vs. operative wound) to decrease risk of wound infection
- types of drains
 - open (Penrose), higher risk of infection
 - closed (Jackson-Pratt, Blake) connected to suction
 - sump (Davol) suction with airflow system to prevent obstruction
- monitor drain outputs daily
- drains should be removed once drainage is minimal (usually less than 30-50 cc/24hr)

WOUND INFECTION

Etiology

- S. aureus*, *E. coli*, *Enterococcus*, *Streptococcus* spp., *Clostridium* spp.

Risk Factors

- type of procedure:
 - clean (elective, not emergent, not traumatic, no acute inflammation, resp/GI/biliary/GU tracts not entered): <1.5%
 - clean-contaminated (elective entering of resp/GI/biliary/GU tracts): <3%
 - contaminated (nonpurulent inflammation, gross spillage from GI, entry into biliary or GU tracts with infected bile/urine, penetrating trauma <4 hrs old): 5%

Antimicrobial Prophylaxis for Surgery:
An Advisory Statement from the National
Surgical Infection Prevention Project
Clin Infect Dis 2004; 38:1706

Level IV Evidence (Consensus)

General Recommendations from Consensus Panel:

The first antimicrobial dose should be administered via infusion within 60 minutes of the surgical incision and prophylactic antimicrobials should be discontinued within 24 hours postoperatively.

The initial dose should be based on the patient's body weight, adjusted dosing weight, or BMI. If the surgical procedure is still in progress 2 half-lives after the initial dose, another dose should be administered intraoperatively.

General Abdominal Colorectal surgery:

For parenteral antimicrobial prophylaxis, use cefoxitin OR cefotetan OR cefazolin plus metronidazole.

If the patient has a β -lactam allergy, use clindamycin combined with either gentamicin, ciprofloxacin, or aztreonam, OR metronidazole combined with either gentamicin or ciprofloxacin.

Chlorhexidine-Alcohol versus Povidone-Iodine for Surgical-Site Antisepsis

Darouiche RO et al. *NEJM* 2010; 362:18-26

Purpose: To determine whether preoperative skin cleansing with chlorhexidine-alcohol is more protective against infection than povidone-iodine.

Methods: Randomized trial of adults undergoing clean-contaminated surgery in six hospitals to preoperative skin preparation with either chlorhexidine-alcohol scrub or povidone-iodine scrub and paint.

Main outcomes: Any surgical-site infection within 30 days after surgery

Results: A total of 849 subjects (409 in the chlorhexidine-alcohol group and 440 in the povidone-iodine group) qualified for the intention-to-treat analysis. The overall rate of surgical-site infection was significantly lower in the chlorhexidine-alcohol group than in the povidone-iodine group (9.5% vs. 16.1%; $P=0.004$; relative risk, 0.59; 95% confidence interval, 0.41 to 0.85). Chlorhexidine-alcohol was significantly more protective than povidone-iodine against both superficial incisional infections (4.2% vs. 8.6%, $P=0.008$) and deep incisional infections (1% vs. 3%, $P=0.05$) but not against organ-space infections (4.4% vs. 4.5%). Similar results were observed in the per-protocol analysis of the 813 patients who remained in the study during the 30-day follow-up period. Adverse events were similar in the two study groups.

Conclusions: Preoperative cleansing of the patient's skin with chlorhexidine-alcohol is superior to cleansing with povidone-iodine for preventing surgical-site infection after clean-contaminated surgery.

- dirty (purulent inflammation, pre-op perforation of resp/GI/biliary/GU tracts, penetrating trauma >4 hrs old): 33%
- increased risk with procedures >2 hrs long, use of drains
- patient characteristics:
 - age, DM, steroids, immunosuppression, obesity, burn, malnutrition, patient with other infections, traumatic wound, radiation, chemotherapy
- other factors:
 - prolonged preoperative hospitalization, reduced blood flow, break in sterile technique, multiple antibiotics, hematoma, seroma, foreign bodies (drains, sutures, grafts)

Clinical Presentation

- typically fever POD #3-6 (*Streptococcus* and *Clostridium* can present in 24 hrs)
- pain, blanchable wound erythema, induration, frank pus or purulosanguinous discharge, warmth
- complications: fistula, sinus tracts, sepsis, abscess, suppressed wound healing, superinfection, spreading infection to myonecrosis or fascial necrosis (necrotizing fasciitis), wound dehiscence, evisceration, hernia

Prophylaxis

- pre-op antibiotics for all surgeries [cefazolin (Ancef®)/metronidazole (Flagyl®)]:
 - within 1 hour preincision; can re-dose with Ancef® after 4 hrs in the OR
- post-op antibiotics for contaminated and dirty surgeries:
 - no evidence supporting more than 24 hrs of post-op antimicrobial prophylaxis for any case
 - generally no need for post-op antibiotics unless intra-abdominal infection
- normothermia (maintain patient temperature >36°C during OR)
- hyperoxygenation (consider FiO₂ >80 in OR)

Treatment

- re-open affected part of incision, culture wound, pack, heal by secondary intention
- antibiotics only if cellulitis or immunodeficiency
- debride necrotic and non-viable tissue intraoperatively

WOUND HEMORRHAGE/HEMATOMA

- secondary to inadequate surgical control of hemostasis

Risk Factors

- anticoagulant therapy, coagulopathies, thrombocytopenia, DIC, severe liver disease, myeloproliferative disorders, severe arterial hypertension, severe cough

Clinical Features

- pain, swelling, discolouration of wound edges, leakage
- rapidly expanding neck hematoma can compromise airway and is a surgical emergency

Treatment

- pressure dressing
- if significant bleeding, may need to re-operate to find source

SEROMA

- fluid collection other than pus or blood
- secondary to transection of lymph vessels
- delays healing

Treatment

- pressure dressing \pm needle drainage
- if significant may need to re-operate

WOUND DEHISCENCE

- disruption of fascial layer, abdominal contents contained by skin only

Clinical Features

- typically POD #1-3, most common presenting sign is serosanguinous drainage from wound, \pm evisceration (disruption of all abdominal layers and extrusion of abdominal contents – mortality of 15%)
- palpation of wound edge: should normally feel a "healing ridge" from abdominal wall closure (raised area of tissue under incision)

Risk Factors

- local: technical failure of closure, increased intra-abdominal pressure (e.g. COPD, ileus, bowel obstruction), hematoma, infection, poor blood supply, radiation
- systemic: smoking, malnutrition (hypoalbuminemia, vitamin C), connective tissue diseases, immunosuppression (disease, steroids, chemotherapy), other (age, DM, sepsis, uremia)

Treatment

- may consider conservative management
- operative closure, evisceration is a surgical emergency

Urinary and Renal Complications

URINARY RETENTION

- may occur after any operation with general anesthesia or spinal anesthesia
- more likely in older males with history of benign prostatic hyperplasia (BPH), patients on anticholinergics

Clinical Presentation

- abdominal discomfort, palpable bladder, overflow incontinence

Treatment

- Foley catheter to rest bladder, then trial of void

OLIGURIA/ANURIA (see also [Nephrology](#), NP20)**Etiology**

- pre-renal vs. renal vs. post-renal:
 - most common post-op cause is pre-renal ± ischemic ATN
 - ♦ external fluid loss: hemorrhage, dehydration, diarrhea
 - ♦ internal fluid loss: third-spacing due to bowel obstruction, pancreatitis, post-op

Clinical Presentation

- urine output <0.5 cc/kg/hr, increasing Cr, increasing BUN

Treatment

- according to underlying cause; fluid deficit is treated with crystalloid, [normal saline (NS) or Ringer's lactate (RL)]

Postoperative Dyspnea

- see *Respiratory Complications*, GS9 and *Cardiac Complications*, GS11
- respiratory: atelectasis, pneumonia, pulmonary embolus (PE), acute respiratory distress syndrome (ARDS), asthma, pleural effusion
- cardiac: MI, arrhythmia, CHF
- pain

Respiratory Complications

ATELECTASIS

- comprises 90% of post-op pulmonary complications

Clinical Features

- low-grade fever on POD #1, tachycardia, crackles, decreased breath sounds, bronchial breathing, tachypnea

Risk Factors

- COPD, smoking, obesity, elderly persons
- upper abdominal/thoracic surgery, oversedation, significant post-op pain, poor inspiratory effort

Treatment

- pre-operative prophylaxis:
 - smoking cessation (most beneficial if >6 weeks pre-op)
- postoperative prophylaxis:
 - minimize use of respiratory depressant drugs
 - good pain control
 - incentive spirometry, deep breathing and coughing, chest physiotherapy, postural changes
 - early ambulation

PNEUMONIA/PNEUMONITIS

- may be secondary to aspiration of gastric contents during anesthetic induction or extubation, causing a chemical pneumonitis

Risk Factors

- aspiration: general anesthetic, decreased LOC, GERD, full stomach, bowel/gastric outlet obstruction + non-functioning NG tube, pregnancy, seizure disorder
- non-aspiration: atelectasis, immobility, pre-existing respiratory disease

Clinical Features

- productive cough, fever
- tachycardia, cyanosis, respiratory failure, decreased LOC
- CXR: pneumonic infiltrate

Treatment

- aspiration prophylaxis: pre-op NPO/NG tube, rapid sequence anesthetic induction
- immediate removal of debris and fluid from airway
- consider endotracheal intubation and flexible bronchoscopic aspiration
- IV antibiotics to cover oral nosocomial aerobes and anaerobes (e.g. cefotaxime, metronidazole)

PULMONARY EMBOLUS (see Respirology, R18)**Clinical Features**

- unilateral leg swelling and pain (DVT as a source of PE), sudden onset SOB, tachycardia, fever (POD #7-10)

Treatment

- IV heparin, long term warfarin (INR = 2-3) for 3 months
- Greenfield (IVC) filter if contraindications to anticoagulation
- prophylaxis: subcutaneous heparin (5000 units bid) or LMW heparin, compression stockings (TED stockings)

PULMONARY EDEMA**Etiology**

- cardiogenic vs. noncardiogenic
- circulatory overload: excess volume replacement, LV failure, shift of fluid from peripheral to pulmonary vascular bed, negative airway pressure, alveolar injury due to toxins (e.g. ARDS)
 - more common with pre-existing cardiac disease
- negative pressure pulmonary edema due to inspiratory efforts against a closed glottis upon awakening from general anaesthesia

Clinical Features

- SOB, crackles at lung bases, CXR abnormal

Treatment (LMNOP)

- Lasix
- Morphine (decreases symptoms of dyspnea, venodilator and afterload reduction)
- Nitrates (venodilator)
- Oxygen + non-invasive ventilation
- Position (sit patient up)

RESPIRATORY FAILURE**Clinical Features**

- dyspnea, cyanosis, evidence of obstructive lung disease
- earliest manifestations – tachypnea and hypoxemia (RR >25, pO₂ <60)
- pulmonary edema, unexplained decrease in SaO₂

Treatment

- ABCs, O₂, ± intubation
- bronchodilators, diuretics to treat CHF
- adequate blood pressure to maintain pulmonary perfusion
- if these measures fail to keep PaO₂ >60, consider ARDS

Cardiac Complications

- abnormal ECGs common in post-op period (compare to pre-op ECG)
- common arrhythmias: supraventricular tachycardia (SVT), atrial fibrillation (secondary to fluid overload, PE, MI)

MYOCARDIAL INFARCTION (MI)

- see Cardiology and Cardiovascular Surgery, C25
- surgery increases risk of MI
- incidence:
 - 0.5% in previously asymptomatic men >50 years old
 - 40-fold increase in men >50 years old with previous MI

Risk Factors

- pre-op hypertension, CHF
- previous MI (highest risk ≤6 months, but risk never returns to baseline)
- increased age
- intra-operative hypotension
- operations >3 hrs
- angina

Clinical Features

- majority of cases on day of operation or POD #1-4
- often silent without chest pain, may only present with new-onset CHF (dyspnea), arrhythmias, hypotension

Intra-abdominal Abscess

Definition

- collection of pus walled-off from rest of peritoneal cavity by inflammatory adhesions and viscera

Etiology

- usually polymicrobial: Gram-negative bacteria, anaerobes
- consider Gram-positives if coexistent cellulitis

Risk Factors

- emergency OR
- post-op contaminated OR
- GI surgery with anastomoses
- poor healing risk factors (DM, poor nutrition, etc.)
- may occur POD #3 after laparotomy when fluid re-distribution occurs

Clinical Features

- persistent spiking fever, dull pain, weight loss
- mass difficult to palpate
- peritoneal signs if abscess perforation and secondary peritonitis
- leukocytosis or leukopenia (immunocompromised, elderly)
- co-existing effusion (pleural effusion with subphrenic abscess)
- common sites: pelvis, Morrison's pouch (space between duodenum and liver), subphrenic, paracolic gutters, lesser sac, peri-appendiceal, post-surgical anastomosis, diverticular, psoas

Investigations

- CBC, blood cultures x 2
- CT ± water-soluble contrast
- DRE (pelvic abscess)

Treatment

- IR percutaneous drainage
- debridement of infected soft tissue around infection
- antibiotics to cover aerobes and anaerobes (ampicillin/gentamicin/metronidazole or ciprofloxacin/metronidazole or clindamycin/gentamicin or cefotetan)

Paralytic Ileus

- see *Bowel Obstruction*, GS23

Delirium

- see Psychiatry, PS17 and Neurology, N10

Thoracic Surgery

Esophagus

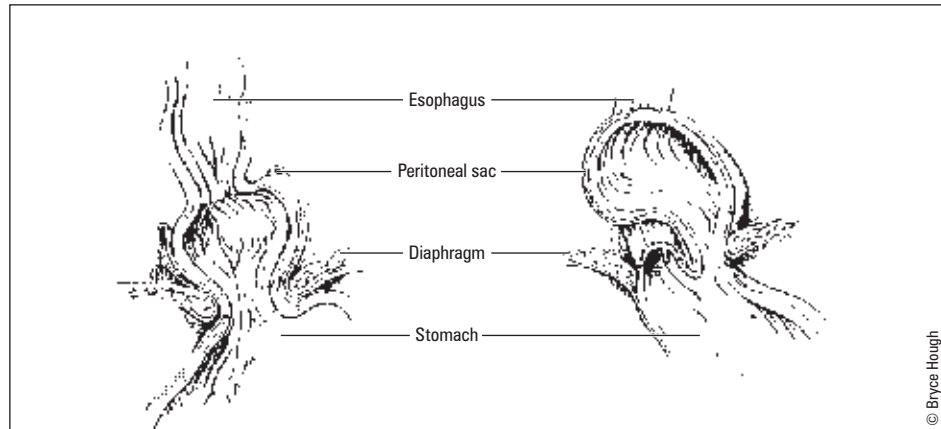


Figure 6. Types of Hiatus Hernia – Sliding (left) and Paraesophageal (right)

SLIDING HIATUS HERNIA (Type I) (see Figure 6)

- herniation of both the stomach and the gastroesophageal (GE) junction into thorax
- 90% of esophageal hernias

Risk Factors

- age
- increased intra-abdominal pressure (e.g. obesity, pregnancy, coughing, heavy lifting, straining with constipation)
- smoking

Clinical Features

- majority are asymptomatic
- larger hernias frequently associated with GERD due to disruption of competence of GE junction and prevention of acid clearance once reflux has occurred

Complications

- most common complication is GERD
- other complications are rare and are related to reflux:
 - esophagitis (dysphagia, heartburn)
 - consequences of esophagitis (peptic stricture, Barrett's esophagus, esophageal carcinoma)
 - extra-esophageal complications (aspiration pneumonia, asthma, cough, laryngitis)

Investigations

- barium swallow, endoscopy, or esophageal manometry (technique for measuring LES pressure) detect larger hernias
- 24-hour esophageal pH monitoring to quantify reflux
- gastroscopy with biopsy to document type and extent of tissue damage and rule out esophagitis, Barrett's, and cancer
- CXR: globular shadow with air-fluid level visible over cardiac shadow

Treatment

- treat symptoms of GERD:
 - lifestyle modification:
 - ♦ stop smoking, weight loss, elevate head of bed, no meals <3 hrs prior to sleeping, smaller and more frequent meals, avoid alcohol, coffee, mint and fat
 - medical:
 - ♦ antacid, H₂-antagonist, proton pump inhibitor, adjuvant prokinetic agent
 - surgical (<15%):
 - ♦ if severe complications or if refractory to medical management
 - ♦ Nissen fundoplication (usually laparoscopic)
 - fundus of stomach is wrapped around the lower esophagus and sutured in place
 - 90% success rate



Differential Diagnosis of Hiatus Hernia

GI Causes	Non-GI Causes
<ul style="list-style-type: none"> • Cholelithiasis • Diverticulitis • Peptic ulcer • Achalasia • Pancreatitis • GERD • Gastritis 	<ul style="list-style-type: none"> • MI • Angina • Pericarditis

PARAESOPHAGEAL HIATUS HERNIA (Type II) (see Figure 6)

- herniation of all or part of the stomach through the esophageal hiatus into the thorax with an undisplaced GE junction
- least common esophageal hernia (<10%)

Clinical Features

- usually asymptomatic due to normal GE junction
- pressure sensation in lower chest, dysphagia

Complications

- hemorrhage, incarceration, strangulation, obstruction, gastric stasis ulcer

Treatment

- surgery to prevent severe complications:
 - reduce hernia and excise hernia sac, repair defect at hiatus, and Nissen fundoplication
 - may consider suturing stomach to anterior abdominal wall (gastropexy)
 - in very elderly patients at high surgical risk consider PEG (percutaneous endoscopic gastrostomy)

MIXED HIATUS HERNIA (Type III)

- combination of Types I and II

TYPE IV HERNIA

- herniation of other abdominal organs into thorax: colon, spleen, small bowel

ESOPHAGEAL PERFORATION**Etiology**

- iatrogenic (most common):
 - endoscopic, dilation, biopsy, intubation, operative, NG tube placement
- barogenic:
 - repeated, forceful vomiting (Boerhaave's syndrome)
 - trauma
 - other: convulsions, defecation, labour (rare)
- ingestion injury:
 - foreign body, corrosive substance
- carcinoma

Clinical Features

- neck or chest pain
- fever, tachycardia, hypotension, dyspnea, respiratory compromise
- subcutaneous emphysema, pneumothorax, hematemesis

Investigations

- CXR: pneumothorax, pneumomediastinum, pleural effusion, subdiaphragmatic air
- CT chest: widened mediastinum, pneumomediastinum
- contrast swallow (water-soluble then thin barium): contrast extravasation

Treatment

- supportive if rupture is contained:
 - NPO, vigorous fluid resuscitation, broad-spectrum antibiotics
- surgical:
 - <24 hrs
 - ♦ primary closure of a healthy esophagus or resection of diseased esophagus
 - >24 hrs or non-viable wound edges
 - ♦ diversion and exclusion followed by delayed reconstruction (i.e. esophagostomy proximally, close esophagus distally, gastrostomy/jejunostomy for decompression/feeding)

Complications

- sepsis, abscess, fistula, empyema, mediastinitis, death
- post-op esophageal leak
- mortality 10-50% dependant on timing of diagnosis



Boerhaave's – transmural esophageal perforation

Mallory-Weiss tear – non-transmural esophageal tear (partial thickness tear)

Both are associated with forceful emesis.

ESOPHAGEAL CARCINOMA

Epidemiology

- male:female = 3:1
- onset 50-60 years of age
- upper (20-33%), middle (33%), lower (33-50%)
- squamous cell carcinoma (SCC) and adenocarcinoma occur with equal frequency, with adenocarcinoma becoming more common

Risk Factors

- geographic variation in incidence
- squamous cell carcinoma (SCC):
 - **4 S's:** Smoking, Spirits (alcohol), Seeds (Betel nut), Scalding (hot liquids)
 - underlying esophageal disease such as strictures, diverticula, achalasia
- adenocarcinoma:
 - Barrett's esophagus (most important), smoking, obesity (increased reflux), GERD

Clinical Features

- frequently asymptomatic – late presentation
- progressive dysphagia (mechanical) – first solids then liquids
- odynophagia then constant pain
- constitutional symptoms
- regurgitation and aspiration (aspiration pneumonia)
- hematemesis, anemia
- tracheoesophageal or bronchoesophageal fistula
- direct, hematogenous or lymphatic spread:
 - trachea (coughing), recurrent laryngeal nerves (hoarseness, vocal paralysis), aortic, liver, lung, bone, celiac and mediastinal nodes
- weight loss

Investigations

- barium swallow:
 - shows narrowing – suggestive but not diagnostic
- esophagoscopy:
 - biopsy/tissue diagnosis
 - determine extent and resectability of tumour
- CT chest/abdomen:
 - visualize local disease
 - staging workup (adrenal, liver, lung, bone metastases)
- endoscopic ultrasound (EUS):
 - visualize local disease
 - regional nodal involvement (most accurate way to stage the cancer)
- bronchoscopy:
 - rule out airway invasion in tumours of the upper and mid esophagus

Treatment

- if inoperable or unresectable (locally invasive disease or distant mets):
 - multimodal therapy:
 - ♦ concurrent external beam radiation and chemotherapy (cisplatin and 5-FU)
 - ♦ possibility of curative esophagectomy after chemoradiation if disease responds well
 - if unable to tolerate multimodal therapy or if highly advanced disease, consider palliative resection, brachytherapy, or endoscopic dilation/stenting/laser ablation for palliation
- if operable:
 - esophagectomy (transthoracic or trans-hiatal approach) and lymphadenectomy
 - ♦ anastomosis in chest or neck
 - ♦ stomach most often used for reconstruction; may also use colon
 - neoadjuvant chemotherapy and radiation are controversial
 - adjuvant chemotherapy ± radiation usually recommended for post-op node-positive disease

Prognosis

- 5-8% operative death rate
- prognosis usually poor because presentation is usually at advanced stage

OTHER DISORDERS

- esophageal varices (see [Gastroenterology, G27](#))
- Mallory-Weiss tear (see [Gastroenterology, G28](#))

Chest Wall

CONGENITAL ABNORMALITIES

- pectus excavatum, pectus carinatum, sternal fissures
- surgery for: cosmesis, psychosocial factors, respiratory or cardiovascular insufficiency

THORACIC OUTLET SYNDROME

- impingement of subclavian vessels and brachial plexus nerve trunk

Etiology

- congenital – cervical rib
- trauma
- degenerative – osteoporosis, arthritis

Clinical Features

- neurogenic – ulnar and median nerve motor and sensory function
- arterial – fatigue, weakness, coldness, ischemic pain, paresthesia
- venous – edema, venous distention, collateral formation, cyanosis

Treatment

- conservative (50 to 90%)
 - physiotherapy, posture and behaviour modification
- surgical – if conservative treatment fails, removal of first or cervical rib (if applicable)

TUMOURS

- benign: fibrous dysplasia, eosinophilic granuloma, osteochondroma
- malignant: fibrosarcoma, chondrosarcoma, osteogenic sarcoma, Ewing's sarcoma, myeloma

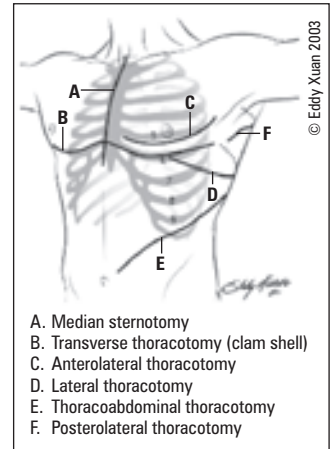


Figure 7. Typical Thoracic Surgery Incisions

Pleura, Lung, and Mediastinum

- see Respirology, R21

TUBE THORACOSTOMY

Indications

- to drain abnormal large-volume air or fluid collections in the pleural space
 - hemothorax, chylothorax, empyema
 - pneumothorax, if:
 - ♦ large or progressive
 - ♦ patient is on mechanical ventilation
 - ♦ bronchopleural fistula
 - ♦ tension pneumothorax
- to facilitate pleurodesis:
 - i.e. obliteration of the pleural space by instilling talc or doxycycline to cause fibrosis and adherence of parietal and visceral pleura
 - indicated for recurrent pleural effusions (often malignant)
- for long-term drainage of malignant effusions

Procedure

- tube size – varies according to indication; larger tube for more viscous drainage
- insertion site – typically 4th or 5th intercostal space in anterior axillary or mid-axillary line
- technique:
 - local anaesthetic
 - ~2 cm skin incision
 - Kelly clamp for blunt dissection to the pleural space, taking care to pass over the top of the rib to avoid neurovascular bundle
 - tube is inserted and sutured in place
 - tube is attached to a pleural drainage system (suction/underwater seal, usually -20 mmH₂O)
 - post-insertion CXR to ensure proper tube placement (posterior apex of lung)
- removal:
 - when drainage <100-200 cc/day, no air leak, and lung is fully expanded
 - consider clamping tube for 4-6 hrs then obtaining CXR to ensure lung remains expanded
 - brisk removal after patient expires and holds breath

Complications

- overall complications are rare (1-3%)
- malposition (most common complication), especially by inexperienced operators:
 - tubes may dissect along the external chest wall, or may be placed below the diaphragm
- bleeding (anticoagulation is a relative contraindication)
- local infection, empyema
- perforation of lung parenchyma
- risk of re-expansion pulmonary edema when large volumes of air or fluid are drawn off quickly (>1.0 to 1.5 L)



Stomach and Duodenum

Peptic Ulcer Disease

GASTRIC ULCERS

- see Gastroenterology, G11, G27

Surgical Treatment

- increasingly rare due to *H. pylori* eradication and medical treatment

Indications for Surgery

- unresponsive to medical treatment (intractability):
 - always operate if fails to heal completely, even if biopsy negative – could be primary gastric lymphoma or adenocarcinoma
- dysplasia or carcinoma:
 - always biopsy ulcer for malignancy
- hemorrhage – 3x greater risk of bleeding compared to duodenal ulcers
- complications: obstruction, perforation, bleeding

Procedures

- distal gastrectomy with ulcer excision – Billroth I or Billroth II (see Figure 8)
- vagotomy and pyloroplasty only if acid hypersecretion – rare
- wedge resection if possible or biopsy with primary repair

DUODENAL ULCERS

- see Gastroenterology, G12
- most within 2 cm of pylorus (duodenal bulb)

Complications

- perforated ulcer (typically on anterior surface)
 - clinical features:
 - ♦ sudden onset of pain (possibly in RLQ due to track down right paracolic gutter)
 - ♦ acute abdomen – rigid, diffuse guarding
 - ♦ ileus
 - ♦ initial chemical peritonitis followed by bacterial peritonitis
 - investigations:
 - ♦ CXR – free air under diaphragm (70% of patients)
 - treatment:
 - ♦ oversew ulcer (plication) and omental (Graham) patch – most common treatment
- posterior penetration:
 - into pancreas → elevated amylase/lipase
 - constant mid-epigastric pain burrowing into back, unrelated to meals
- hemorrhage (typically on posterior surface):
 - gastroduodenal artery involvement
 - treatment:
 - ♦ resuscitation initially with crystalloids; blood transfusion if necessary
 - ♦ diagnostic and/or therapeutic endoscopy (laser, cautery or injection); if recurs, may have 2nd scope
 - ♦ surgery if severe or recurrent bleeding, hemodynamically unstable, or failure of endoscopy
 - oversewing of ulcer, pyloroplasty
- gastric outlet obstruction:
 - etiology: ulcer can lead to edema, fibrosis of pyloric channel, neoplasm
 - clinical presentation:
 - ♦ nausea and vomiting (undigested food, non-bilious), dilated stomach, crampy abdominal pain
 - ♦ succussion splash (splashing noise heard when patient is shaken)
 - ♦ auscultate gas and fluid movement in obstructed organ

- treatment:
 - ♦ NG decompression and correction of hypochloremic, hypokalemic metabolic alkalosis
 - ♦ medical management initially: high dose PPI therapy
 - ♦ if obstruction does not resolve, consider surgical resection: either Billroth I, pyloroplasty or gastrojejunostomy to bypass

Surgical Treatment

- surgical indications:
 - hemorrhage, rebleed in hospital, perforation, gastric outlet obstruction
 - ♦ decision to operate based on amount of blood loss (usually >8 units), rate of bleeding and hemodynamic stability
 - intractable despite medical management (endoscopy)
- procedures:
 - oversewing of ulcer, pyloroplasty
 - vagotomy
 - ♦ rarely done now due to *H. pylori* eradication

Complications of Surgery

- retained antrum
- fistula (gastrocolic/gastrojejunal)
- dumping syndrome, postvagotomy diarrhea, afferent loop syndrome (see *Complications of Gastric Surgery*, GS19)

Gastric Carcinoma

Epidemiology

- male:female = 3:2
- incidence for adenocarcinoma = 10 per 100,000, incidence highest in Asia (Japan 80 times higher than in U.S.)
- most common age group = 50-59 years
- incidence has decreased by 2/3 in past 50 years

Risk Factors

- *H. pylori*, causing chronic atrophic gastritis
- hereditary nonpolyposis colorectal cancer (HNPCC)
- smoking, alcohol, smoked food, nitrosamines
- pernicious anemia associated with achlorhydria and chronic atrophic gastritis
- gastric adenomatous polyps
- previous partial gastrectomy (>10 years post-gastrectomy)
- hypertrophic gastropathy
- blood type A

Clinical Features

- clinical suspicion:
 - ulcer fails to heal
 - lesion on greater curvature of stomach or cardia
- asymptomatic, insidious or late onset of symptoms:
 - postprandial abdominal fullness, vague epigastric pain
 - anorexia, weight loss
 - burping, nausea, vomiting, dyspepsia, dysphagia
 - hepatomegaly, epigastric mass (25%)
 - hematemesis, fecal occult blood, melena, iron-deficiency anemia
- signs of metastatic disease:
 - Virchow's node – left supraclavicular node
 - Blumer's shelf – mass in pouch of Douglas
 - Krukenberg tumour – metastases to ovary
 - Sister Mary Joseph node – umbilical metastases
 - Irish's node – left axillary nodes
- metastasis:
 - liver, lung, brain

Investigations

- OGD and biopsy
- chest/abdo/pelvis CT
- CT for metastatic work-up (see Table 4)

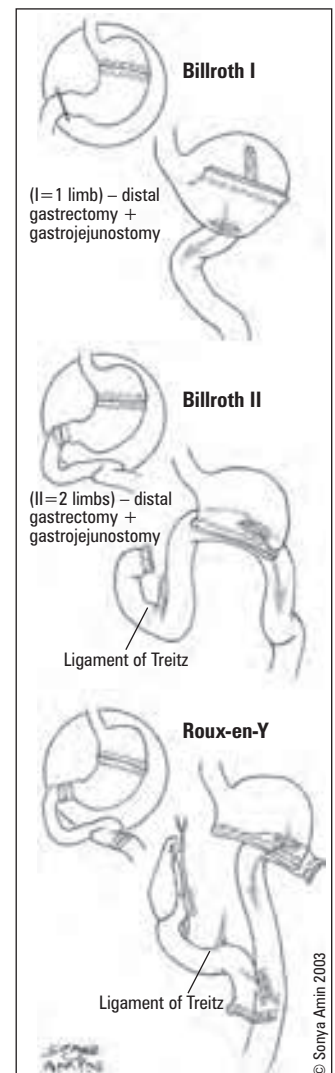


Figure 8. Billroth I and Billroth II with Roux-en-Y Reconstruction (gastrojejunostomy)

Table 4. Staging of Gastric Carcinoma

Stage	Criteria	Prognosis (5-year survival)
I	Mucosa and submucosa	70%
II	Extension to muscularis propria	30%
III	Extension to regional nodes	10%
IV	Distant metastases or involvement of continuous structures	0%

Treatment

- adenocarcinoma:
 - proximal lesions:
 - ♦ total gastrectomy and esophagojejunostomy – Roux-en-Y (see Figure 8)
 - distal lesions:
 - ♦ distal gastrectomy: wide margins, en bloc removal of omentum and lymph nodes
 - palliation:
 - ♦ gastric resection to decrease bleeding and relieve obstruction, enables the patient to eat
 - ♦ radiation therapy
 - ♦ studies are showing larger role for chemotherapy
- lymphoma:
 - chemotherapy ± radiation, surgery in limited cases (perforation, bleeding, obstruction)

Gastric Sarcoma

Gastrointestinal Stromal Tumour (GIST)

- most common mesenchymal neoplasm of GI tract
- derived from interstitial cells of Cajal (cells associated with Auerbach's plexus that have autonomous pacemaker function co-ordinate peristalsis throughout the GI tract)
- 75-80% associated with tyrosine kinase (c-KIT) mutations
- most common in stomach (50%), and proximal small intestine (25%), but can occur anywhere along GI tract
- typically present with vague abdominal mass, feeling of abdominal fullness, or with secondary symptoms of bleeding and anemia
- often discovered incidentally on CT, laparotomy or endoscopy

Risk Factors

- Carney's Triad: GISTs, paraganglioma, and pulmonary chondroma
- Type IA neurofibromatosis

Management

- surgical resection if >2 cm; follow with serial endoscopy if <2 cm then resect if growing or symptomatic
- pre-operative biopsy: controversial, but useful for indeterminate lesions:
 - not recommended if index of suspicion for GIST is high
 - percutaneous biopsy is NOT recommended due to high friability and risk of peritoneal spread
- localized GIST: surgical resection with preservation of intact pseudocapsule
 - lymphadenectomy NOT recommended, as GISTs rarely metastasize to lymph nodes
- advanced disease: metastases to liver and/or peritoneal cavity:
 - chemotherapy with imatinib mesylate (tyrosine kinase inhibitor)
 - current research looking into role of imatinib as adjuvant or neoadjuvant therapy for localized GIST

Prognosis

- risk of metastatic potential depends on:
 - tumour size (worse if >10 cm)
 - mitotic activity (worse if >5 mitotic figures or 50/hpf)
 - degree of nuclear pleomorphism
 - location: with identical sizes, extra-gastric location has a higher risk of progression than GISTs in the stomach
 - mets to liver, omentum, peritoneum; nodal mets rare

Bariatric Surgery

- weight reduction surgery for morbid obesity
- indications: BMI >40 or BMI >35 with related comorbidity (e.g. DM, CAD)
- requires multidisciplinary evaluation and follow-up

Bariatric (Weight Loss) Surgery for Obesity is considered when Other Treatments have Failed
Benefits

- Greater weight loss in patients with BMI >30 at 2 years
- Reduction in co-morbidities (Type II diabetes, hypertension and medication use)
- Improvement in quality of life at 2 years (physical function, physical role, general health, vitality and emotional role)

Risks

- Complications: leaks, hernias, infection, pulmonary embolism, postoperative mortality
- Side effects specific to type of procedure (i.e. vomiting, dumping syndrome, food intolerance)
- Cholecystitis occurs as a result of rapid weight loss

Colquitt JL, Picot J, Loveman E, Clegg AJ. Surgery for Obesity (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2009. Chichester, UK: John Wiley & Sons, Ltd.

Surgical Options

- malabsorptive/restrictive:
 - laparoscopic Roux-en-Y gastric bypass (most common)
 - staple off small gastric pouch (restrictive) with Roux-en-Y limb to pouch (malabsorptive) with dumping syndrome physiology
 - most effective, higher complication rates
- restrictive:
 - laparoscopic adjustable gastric banding
 - silicone band around fundus creates pouch, adjustable through port under skin
 - laparoscopic vertical banded gastroplasty
 - vertical stapled small gastric pouch with placement of silastic ring band
- malabsorptive:
 - biliopancreatic diversion with duodenal switch
 - gastrectomy, enteroenterostomy, duodenal division closure and duodenoenterostomy

Complications

- perioperative mortality ~1% (anastomotic leak with peritoneal signs, PE)
- obstruction at enteroenterostomy (see *Complications of Gastric Surgery*, below)
- staple line dehiscence
- dumping syndrome
- cholethiasis due to rapid weight loss (20-30%)
- band abscess (if long-term)

Complications of Gastric Surgery

- most resolve within 1 year (see Figure 9)

Alkaline Reflux Gastritis (see Figure 9A)

- duodenal contents (bilious) reflux into stomach causing gastritis ± esophagitis
- treatment:
 - medical: H₂-blocker, metoclopramide, cholestyramine (bile acid sequestrant)
 - surgical: conversion of Billroth I or II to Roux-en-Y

Afferent Loop Syndrome (see Figure 9B)

- accumulation of bile and pancreatic secretions causes intermittent mechanical obstruction and distention of afferent limb
- clinical features:
 - early postprandial distention, RUQ pain, nausea, bilious vomiting, anemia
- treatment: surgery (conversion to Roux-en-Y increases afferent loop drainage)

Dumping Syndrome (see Figure 9C)

- early – 15 minutes post-prandial:
 - etiology:
 - hyperosmotic chyme released into small bowel (fluid accumulation and jejunal distention)
 - clinical features:
 - post-prandial symptoms
 - epigastric fullness or pain, emesis, nausea, diarrhea, palpitations, dizziness, tachycardia, diaphoresis
 - treatment:
 - small multiple low carbohydrate, low fat and high protein meals and avoidance of liquids with meals
 - last resort is interposition of antiperistaltic jejunal loop between stomach and small bowel to delay gastric emptying
- late – 3 hours post-prandial:
 - etiology: large glucose load leads to large insulin release and hypoglycemia
 - treatment: small snack 2 hours after meals

Blind-Loop Syndrome (see Figure 9D)

- bacterial overgrowth of colonic Gram-negative bacteria in afferent limb
- clinical features:
 - anemia/weakness, diarrhea, malnutrition, abdominal pain and hypocalcemia
- treatment: broad-spectrum antibiotics, surgery (conversion to Billroth I)

Postvagotomy Diarrhea (see Figure 9E)

- up to 25%
- bile salts in colon inhibit water resorption
- treatment: medical (cholestyramine), surgical (reversed interposition jejunal segment)

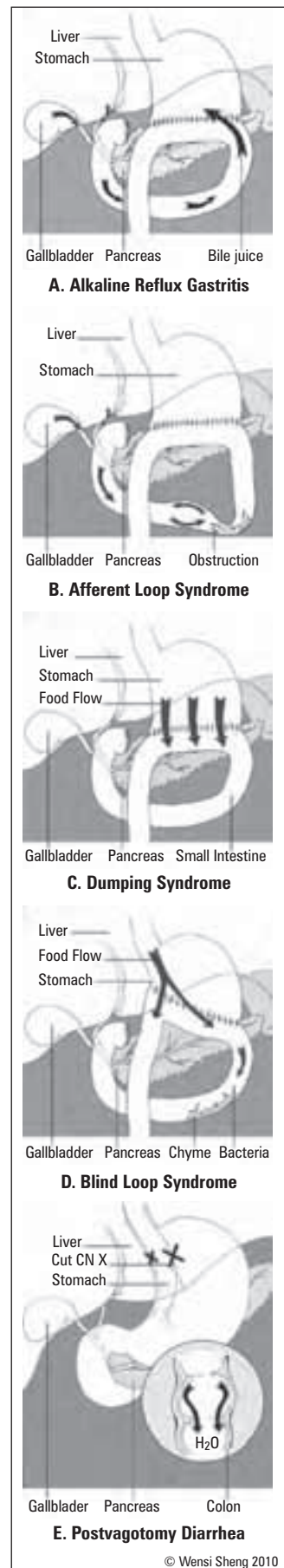


Figure 9. Complications of Gastric Surgery
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Small Intestine

Meckel's Diverticulum

- remnant of the embryonic vitelline duct on antimesenteric border of ileum
- heterotopic – several types of mucosa including gastric, pancreatic, colonic
- most common true diverticulum of GI tract

Clinical Features

- 2% symptomatic
- GI bleed, small bowel obstruction (SBO), diverticulitis (mimics appendicitis)
- painless bleeding – ulceration caused by ectopic gastric mucosa
 - 50% of patients with this presentation are <2 years old

Investigations

- technetium-99 to identify the ectopic gastric mucosa (Meckel's scan)

Complications

- fistula: umbilicus-ileum, umbilical sinus
- fibrous cord between umbilicus and ileum
- SBO due to volvulus, intussusception, perforation

Treatment

- incidental finding – consider surgical resection
- symptomatic – fluid and electrolyte stabilization and surgical resection
- broad based – segmental resection to remove all mucosal types and ulcerated mucosa opposite the diverticulum (i.e. not simple diverticulectomy)



Rule of 2s for Meckel's Diverticulum

- 2% of the population
- Symptomatic in 2% of cases
- Found within 2 feet (10-90 cm) of the ileocecal (IC) valve
- 2 inches in length
- Often present by 2 years of age



Tumours of Small Intestine

Risk Factors

- carcinogen exposure (red meat in diet)
- familial adenomatous polyposis (FAP), Peutz-Jegher syndrome, Gardner's syndrome
- Crohn's disease, celiac disease
- immunodeficiency, autoimmune disorders

Clinical Features

- usually asymptomatic until advanced
- intermittent obstruction, intussusception, occult bleeding, palpable abdominal mass, abdominal pain

BENIGN TUMOURS

- 10x more common than malignant
- usually asymptomatic until large
- most common sites: terminal ileum, proximal jejunum
- polyps:
 - adenomas
 - familial adenomatous polyposis (FAP) (see *Familial Colon Cancer Syndromes*, GS33)
 - hamartomatous
 - juvenile polyps
- other: leiomyomas, lipomas, hemangiomas

MALIGNANT TUMOURS

- usually asymptomatic until advanced stage
 - 25-30% associated with distant metastases at time of diagnosis
- adenocarcinoma:
 - most common primary tumour of small intestine
 - usually 50-70 years old, male predominance
 - usually in proximal small bowel, incidence decreases distally
 - risk factors: Crohn's disease, FAP
 - early metastasis to lymph nodes – 80% metastatic at time of operation
 - investigations – CT abdo/pelvis, endoscopy
 - treatment – surgical resection ± chemotherapy
 - 5-year survival 25%



Malignant Tumours

Adenocarcinoma	Most common
Carcinoid	
Lymphoma	
Sarcoma	Least common

- **carcinoid:**

- increased incidence 50-60 years old
- originate from enterochromaffin cell in crypts
- most commonly 60 cm from the ileocecal (IC) valve
 - ♦ appendix 46%, distal ileum 28%, rectum 17%
- often slow-growing
- classified by embryological origin (correlate with morphology, biological behaviour):
 - ♦ foregut – stomach, duodenum, pancreas
 - ♦ midgut – jejunum, ileum, appendix, ascending colon
 - ♦ hindgut – transverse, descending and sigmoid colon, rectum
- clinical features:
 - ♦ usually asymptomatic, incidental finding
 - ♦ obstruction, bleeding, crampy abdominal pain, intussusception
 - ♦ carcinoid syndrome (<10%):
 - hot flashes, hypotension, diarrhea, bronchoconstriction (wheezing), tricuspid/pulmonic valve insufficiency, right heart failure
 - requires liver involvement: lesion secretes serotonin, kinins and vasoactive peptides directly to systemic circulation (normally inactivated by liver)
 - EXCEPTION: carcinoid tumours arising in the bronchi can cause carcinoid syndrome without liver involvement because of access to systemic circulation
- investigations:
 - ♦ most found incidentally at surgery for obstruction or appendectomy
 - ♦ elevated 5-HIAA (breakdown product of serotonin) in urine or increased 5-HT in blood
- treatment:
 - ♦ tumour and metastases: surgical resection ± chemotherapy
 - ♦ carcinoid syndrome: steroids, histamine, octreotide
- prognosis:
 - ♦ metastatic risk 2% if size <1 cm, 90% if >2 cm
 - ♦ 5-year survival 70%; 20% with liver metastases

- **lymphoma:**

- highest incidence at 70 years old, more common in males
- usually non-Hodgkin's lymphoma
- location:
 - ♦ usually distal ileum
 - ♦ proximal jejunum in patients with celiac disease
- clinical features:
 - ♦ fatigue, weight loss, abdominal pain, fever, malabsorption
 - ♦ rarely – perforation, obstruction, bleeding, intussusception
- treatment:
 - ♦ low grade: chemotherapy with cyclophosphamide
 - ♦ high grade: surgical resection, radiation
 - ♦ palliative: somatostatin, doxorubicin
- 5-year survival 40%

- **metastatic:**

- most common site of GI metastases in patients with metastatic melanoma
- hematogenous spread from breast, lung, kidney
- direct extension from cervix, ovaries, colon

- **gastrointestinal stromal tumours (GISTs):**

- see *Gastric Sarcoma* section, GS18


Symptoms of Carcinoid Syndrome

Flushing
Diarrhea
Right-sided heart failure

Ability of Somatostatin Receptor Scintigraphy to Identify Patients with Gastric Carcinoids: A Prospective Study

J Nucl Med 2000; 41(10):1646-56

Background: Carcinoid tumours are challenging cancers to identify, with low detection rates achieved by conventional radiologic imaging modalities. Somatostatin receptor scintigraphy (SRS) is a new imaging modality which has been shown to have improved rates of detection of carcinoid tumours compared to conventional imaging studies. The purpose of this study was to determine the sensitivity and specificity of SRS in identifying gastric carcinoids.

Methods: 162 consecutive patients with Zollinger-Ellison syndrome (ZES) were studied prospectively. Patients were investigated by annual SRS with SPECT, upper gastrointestinal endoscopy, and direct biopsies of any detected gastric abnormalities, as well as random gastric tissue biopsies. Results of SRS were correlated with the gastric biopsy results.

Results: Gastric SRS localization was positive in 19 (12%) of 162 patients. Sixteen patients had a gastric carcinoid, and 12 of these patients had SRS localization. The sensitivity of SRS in localizing a gastric carcinoid was 75%, with a specificity of 95%. Positive and negative predictive values were 63% and 97%, respectively.

Conclusion: SRS is a noninvasive method which can be used to identify gastric carcinoid tumours with high specificity and reasonable sensitivity.

Hernia

Definition

- fascial defect → protrusion of a viscus into an area in which it is not normally contained

Epidemiology

- male:female = 9:1
- lifetime risk of developing a hernia: males 20-25%, females 2%
- 50% are indirect inguinal hernia, 25% are direct inguinal hernia, 5% are femoral
- most common surgical disease of males

Risk Factors

- activities which increase intra-abdominal pressure:
 - obesity, chronic cough, pregnancy, constipation, straining on urination or defecation, ascites, heavy lifting
- congenital abnormality (e.g. patent processus vaginalis)
- previous hernia repair

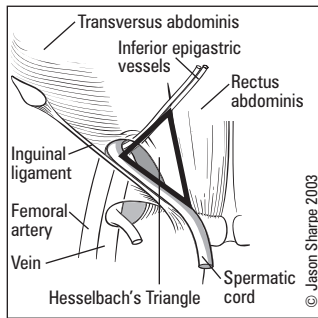


Figure 10. Normal Inguinal Anatomy

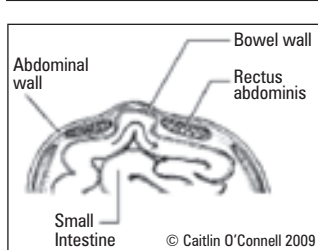
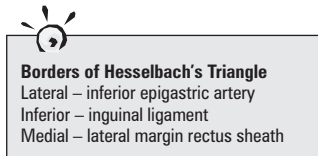


Figure 11. Richter's Hernia

Clinical Features

- mass of variable size
- tenderness worse at end of day, relieved with supine position or with reduction
- abdominal fullness, vomiting, constipation
- transmits palpable impulse with coughing or straining

Investigations

- physical examination usually sufficient
- ultrasound \pm CT

Classification

- complete – hernia sac and contents protrude through defect
- incomplete – partial protrusion through the defect
- internal hernia – sac herniating into or involving intra-abdominal structure
- external hernia – sac protrudes completely through abdominal wall
- strangulated hernia – vascular supply of protruded viscus is compromised (ischemia)
 - requires **emergency** repair
- incarcerated hernia – irreducible hernia, not necessarily strangulated
- Richter's hernia – only part of circumference of bowel (usually anti-mesenteric border) is incarcerated or strangulated so may not be obstructed
 - a strangulated Richter's hernia may self-reduce and thus be overlooked, leaving a gangrenous segment at risk of perforation
- sliding hernia – part of wall of hernia formed by protruding viscus (usually cecum, sigmoid colon, bladder)

Anatomical Types

- groin (see Tables 5 and 6)
 - indirect and direct inguinal, femoral (see Figure 12)
 - pantaloon: combined direct and indirect hernias, peritoneum draped over inferior epigastric vessels
- epigastric: defect in linea alba above umbilicus
- incisional: ventral hernia at site of wound closure, may be secondary to wound infection
- other: Littre's (involving Meckel's), Amyand's (containing ruptured appendix), lumbar, obturator, parastomal, umbilical, Spigelian (ventral hernia through linea semilunaris)

Complications

- incarceration: irreducible
- strangulation: irreducible with resulting ischemia:
 - small, new hernias more likely to strangulate
 - femoral \gg indirect inguinal $>$ direct inguinal
 - intense pain followed by tenderness
 - intestinal obstruction, gangrenous bowel, sepsis
 - surgical emergency
 - **DO NOT** attempt to manually reduce hernia if septic or if contents of hernial sac gangrenous

Treatment

- surgical treatment (herniorrhaphy) is only to prevent strangulation and evisceration or for cosmesis or symptoms; if asymptomatic can delay surgery
- repair may be done open or laparoscopic and may use mesh for tension-free closure
- most repairs are now done with a plug in the hernial defect and a patch over it or patch alone
- observation is acceptable for small asymptomatic inguinal hernias

Postoperative Complications

- recurrence (15-20%):
 - risk factors: recurrent hernia, age >50 , smoking, BMI >25 , poor pre-op functional status (ASA ≥ 3 – see [Anaesthesia](#), A4), associated medical conditions: type II DM, hyperlipidemia, immunosuppression, any comorbid conditions increasing intra-abdominal pressure
 - less common with mesh/"tension-free" repair
- scrotal hematoma (3%):
 - painful scrotal swelling from compromised venous return of testes
 - deep bleeding – may enter retroperitoneal space and not be initially apparent
 - difficulty voiding
- nerve entrapment:
 - ilioinguinal
 - genital branch of genitofemoral (in spermatic cord)
- stenosis/occlusion of femoral vein:
 - acute leg swelling
- ischemic colitis

Groin Hernias

Table 5. Groin Hernias

	Direct Inguinal	Indirect Inguinal	Femoral
Epidemiology	1% of all men	Most common hernia in men and women Males > females	Affects mostly females
Etiology	Acquired weakness of transversalis fascia "Wear and tear" Increased intra-abdominal pressure	Congenital persistence of processus vaginalis in 20% of adults	Pregnancy – weakness of pelvic floor musculature Increased intra-abdominal pressure
Anatomy	Through Hesselbach's triangle Medial to inferior epigastric artery Usually does not descend into scrotal sac	Originates in deep inguinal ring Lateral to inferior epigastric artery Often descends into scrotal sac (or labia majora)	Into femoral canal, below inguinal ligament but may override it Medial to femoral vein within femoral canal
Treatment	Surgical repair	Surgical repair	Surgical repair
Prognosis	3-4% risk of recurrence	<1% risk of recurrence	

Table 6. Superficial Inguinal Ring vs. Deep Inguinal Ring

Superficial Inguinal Ring	Deep Inguinal Ring
Opening in ext. abdominal aponeurosis; palpable superior and lateral to pubic tubercle	Opening in transversalis fascia; palpable superior to mid-inguinal ligament
Medial border: medial crus of ext. abdominal aponeurosis	Medial border: inf. epigastric vessels
Lateral border: lateral crus of ext. oblique aponeurosis	Superior-lateral border: internal oblique and transversus abdominis muscles
Roof: intercrural fibres	Inferior border: inguinal ligament

Bowel Obstruction

Definition

- partial or complete blockage of the bowel resulting in failure of intestinal contents to pass through lumen

Pathogenesis

- disruption of the normal flow of intestinal contents → proximal dilation + distal decompression
- may take 12-24 hrs to decompress, therefore passage of feces and flatus may occur after the onset of obstruction
- bowel ischemia may occur if blood supply is strangulated or bowel wall inflammation leads to venous congestion
- bowel wall edema and disruption of normal bowel absorptive function → increased intraluminal fluid → transudative fluid loss into peritoneal cavity, electrolyte disturbances

Differential Diagnosis

- small bowel obstruction (SBO), large bowel obstruction (LBO), pseudo-obstruction

Clinical Features

- must differentiate between obstruction and ileus, and characterize obstruction as acute vs. chronic, partial vs. complete (constipation vs. obstipation), small vs. large bowel, strangulating vs. non-strangulating, and with vs. without perforation

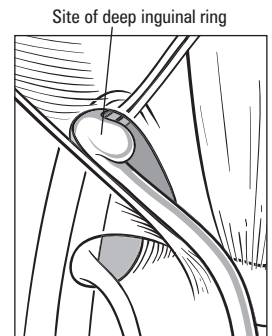
Table 7. Bowel Obstruction vs. Paralytic Ileus

	SBO	LBO	Paralytic ileus
Nausea, Vomiting	Early, may be bilious	Late, may be feculent	Present
Abdominal Pain	Colicky	Colicky	Minimal or absent
Abdominal Distention	+ (prox) < ++ (distal)	++	+
Constipation	+	+	+
Other	± visible peristalsis	± visible peristalsis	
Bowel Sounds	Normal, increased Absent if secondary ileus	Normal, increased (borborygmi) Absent if secondary ileus	Decreased, absent
AXR Findings	Air-fluid levels "Ladder" pattern (plicae circularis) Proximal distention (>3 cm) + no colonic gas	Air-fluid levels "Picture frame" appearance Proximal distention + distal decompression No small bowel air if competent ileocecal valve Coffee bean sign	Air throughout small bowel and colon

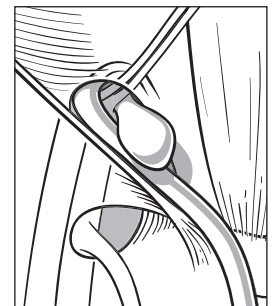


Contents of Spermatic Cord

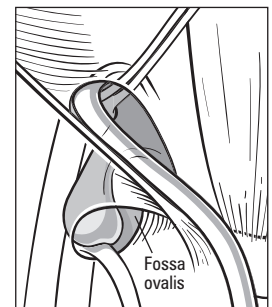
vas deferens, testicular artery/veins, genital branch of genitofemoral nerve, lymphatics, cremaster muscle, ± hernia sac



Indirect hernia



Direct hernia



Femoral hernia

© Jason Sharpe 2003

Figure 12. Schematic of Inguinal (Direct and Indirect) and Femoral Hernias

Complications (of total obstruction)

- strangulating obstruction (10% of bowel obstructions) = **surgical emergency**:
 - cramping pain turns to continuous ache, hematemesis, melena (if infarction)
 - fever, leukocytosis, tachycardia
 - peritoneal signs, early shock
 - see also *Intestinal Ischemia*, GS27
- other:
 - perforation: secondary to ischemia and luminal distention
 - septicemia
 - hypovolemia (due to third spacing)

**Increased Risk of Perforation with Distention as seen on Abdo Imaging**

Small bowel ≥ 3 cm
Distal colon ≥ 6 cm
Proximal colon ≥ 9 cm
Cecum ≥ 12 cm

Investigations

- radiological:
 - upright CXR or left lateral decubitus (LLD) to rule out free air, usually seen under the right hemidiaphragm
 - abdominal x-ray (3 views) to determine SBO vs. LBO vs. ileus (see Table 7)
 - ♦ if ischemic bowel look for: free air, pneumatosis, thickened bowel wall, air in portal vein, dilated small and large bowels, thickened or hose-like haustra (normally fingerlike projections)
 - other:
 - ♦ CT provides information on level of obstruction, severity, cause
 - ♦ upper GI series/small bowel series for SBO (if no cause apparent, i.e. no hernias, no previous surgeries)
 - ♦ if suspect LBO, consider a rectal water-soluble (Gastrografin® for PO/PR; Hypaque® for IV) enema rather than barium enema (can thicken and cause complete obstruction)
 - ♦ may consider ultrasound or MRI in pregnant patients
- laboratory:
 - may be normal early in disease course
 - BUN, creatinine, hematocrit (hemoconcentration) to assess degree of dehydration
 - fluid, electrolyte abnormalities
 - amylase elevated
 - metabolic alkalosis due to frequent emesis
 - if strangulation: leukocytosis with left shift, lactic acidosis, elevated LDH (late signs)

Treatment

- stabilize vitals, fluid and electrolyte resuscitation (with normal saline/Ringer's first, then with added potassium after fluid deficits are corrected)
- NG tube to relieve vomiting, prevent aspiration and decompress small bowel by prevention of further distention by swallowed air
- Foley catheter to monitor in/outs

Small Bowel Obstruction (SBO)

Etiology**Table 8. Common Causes of SBO**

Intraluminal	Intramural	Extramural
Intussusception	Crohn's	Adhesions
Gallstones	Radiation stricture	Incarcerated hernia
	Adenocarcinoma	Peritoneal carcinomatosis

Treatment

- consider whether complete or partial obstruction, ongoing or impending strangulation, location and cause:
 - SBO with history of abdo/pelvic surgery → conservative management (likely to resolve) → surgery if no resolution in 48-72 hrs or complications
 - complete SBO, strangulation → urgent surgery after stabilizing patient
 - trial of medical management may be indicated in Crohn's, recurrent SBO, carcinomatosis
 - special case: early postoperative SBO (within 30 days of abdominal surgery) – prolonged trial of conservative therapy is appropriate, surgery is reserved for complications such as strangulation

Prognosis

- mortality: non-strangulating <1%, strangulating 8% (25% if >36 hours), ischemic = up to 50%

**Top 3 Causes of SBO (in order)****ABC**

1. Adhesions
2. Bulge (hernias)
3. Cancer (neoplasms)

Large Bowel Obstruction (LBO)

Etiology

Table 9. Common Causes of LBO

Intraluminal	Intramural	Extramural
Constipation	Adenocarcinoma Diverticulitis IBD stricture Radiation stricture	Volvulus



Top 3 Causes of LBO (in order)

1. Cancer
2. Diverticulitis
3. Volvulus

Clinical Features (unique to LBO)

- open loop (10-20%) (safe):
 - incompetent ileocecal valve allows relief of colonic pressure as contents reflux into ileum, therefore clinical presentation similar to SBO
- closed loop (80-90%) (**dangerous**):
 - competent ileocecal valve, resulting in proximal and distal occlusions
 - massive colonic distention → increased pressure in cecum → bowel wall ischemia → necrosis → perforation



In a patient with clinical LBO consider impending perforation when:

- Cecum ≥ 12 cm in diameter
- Tenderness present over cecum

Treatment

- surgical correction of obstruction (usually requires resection + temporary diverting colostomy)
- volvulus requires sigmoidoscopic or endoscopic decompression followed by operative reduction if unsuccessful
 - if successful, consider sigmoid resection on same admission

Prognosis

- overall mortality: 10%
- cecal perforation + feculent peritonitis: 20% mortality

Pseudo-Obstruction

Definition

- condition with symptoms of intestinal blockage without any physical signs of blockage

Differential Diagnosis

- acute: toxic megacolon, trauma, postoperative, neurologic disease, retroperitoneal disease
- chronic: neurologic disease (enteric, central, peripheral nervous system), scleroderma

Toxic Megacolon



Pathogenesis

- extension of inflammation into smooth muscle layer causing paralysis
- damage to myenteric plexus and electrolyte abnormalities are not consistently found

Etiology

- inflammatory bowel disease (ulcerative colitis > Crohn's Disease)
- infectious colitis: bacterial (*C. difficile*, *Salmonella*, *Shigella*, *Campylobacter*), viral (cytomegalovirus), parasitic (*E. histolytica*)
- volvulus, diverticulitis, ischemic colitis, obstructing colon cancer are rare causes

Clinical Features

- infectious colitis usually present for >1 week before colonic dilatation
- diarrhea \pm blood (but improvement of diarrhea may portend onset of megacolon)
- abdominal distention, tenderness, \pm local/general peritoneal signs (suggest perforation)
- triggers: hypokalemia, constipating agents (opioids, antidiarrheals, loperamide, anticholinergics), barium enema, colonoscopy

Diagnostic Criteria

- must have both colitis and systemic manifestations for diagnosis
- radiologic evidence of dilated colon
- **three of:** fever, HR >120, WBC >10.5, anemia
- **one of:** fluid and electrolyte disturbances, hypotension, altered LOC



Use caution when giving antidiarrheals, especially with bloody diarrhea.

Investigations

- CBC (leukocytosis with left shift, anemia from bloody diarrhea), electrolytes, elevated CRP, ESR
- metabolic alkalosis (volume contraction and hypokalemia) and hypoalbuminemia are late findings
- AXR: dilated colon >6 cm (right > transverse > left), loss of haustra
- CT: useful to assess underlying disease

Treatment

- NPO, NG tube, stop constipating agents, correct fluid and electrolyte abnormalities, transfusion
- serial AXRs
- broad-spectrum antibiotics (reduce sepsis, anticipate perforation)
- aggressive treatment of underlying disease (e.g. steroids in IBD, metronidazole for *C. difficile*)
- indications for surgery (50% improve on medical management):
 - worsening or persisting toxicity or dilation after 48-72 hrs
 - severe hemorrhage, perforation
- procedure: subtotal colectomy + end ileostomy with 2nd operation for re-anastomosis

Prognosis

- average 25-30% mortality

Paralytic Ileus

Pathogenesis

- temporary paralysis of the myenteric plexus

Associations

- postoperative, intra-abdominal sepsis, medications (opiates, anesthetics, psychotropics), electrolyte disturbances (Na, K, Ca), *C. difficile*, inactivity

Treatment

- NG decompression, NPO, fluid resuscitation, correct causative abnormalities (e.g. sepsis, medications, electrolytes), consider TPN for prolonged ileus
- post-op: gastric and small bowel motility returns by 24-48 hrs, colonic motility by 3-5 d
- current interest in novel therapies such as gum chewing and pharmacologic therapy (opioid antagonists, neostigmine)

Ogilvie's Syndrome

- acute pseudo-obstruction
- distention of colon without mechanical obstruction in distal colon
- arises in bedridden patients with serious extraintestinal illness or trauma
- exact mechanism unknown, likely autonomic motor dysregulation → possibly sympathetic deprivation to colon, unopposed parasympathetic tone, and interruption of sacral parasympathetic tone to distal bowel
- first presents with abdominal distention (>90%) ± tenderness
- later symptoms mimic true obstruction

Associations

- most common: trauma, infection, cardiac (MI, CHF)
- disability (long term debilitation, chronic disease, bed-bound nursing home patients, paraplegia), drugs (narcotic use, laxative abuse, polypharmacy), other (recent orthopaedic or neurosurgery, post-partum, hypokalemia, retroperitoneal hematoma, diffuse carcinomatosis)

Investigations

- AXR: cecal dilatation – if diameter ≥ 12 cm, increased risk of perforation

Treatment

- treat underlying cause
- NPO, NG tube
- decompression: rectal tube, colonoscopy, neostigmine (cholinergic drug), surgical decompression (ostomy/resection) uncommon
- surgery (extremely rare): if perforation, ischemia or failure of conservative management

Prognosis

- most resolve with conservative management

Intestinal Ischemia

Etiology

- acute:
 - arterial:
 - ♦ occlusive: thrombotic, embolic, extrinsic compression (e.g. strangulating hernia)
 - ♦ non-occlusive: mesenteric vasoconstriction 2° to systemic hypoperfusion (preserves supply to vital organs)
 - ♦ trauma/dissection
 - venous thrombosis (prevents venous outflow): consider hypercoagulable state, deep vein thrombosis (DVT)
- chronic: usually due to atherosclerotic disease – look for CVD risk factors

Clinical Features

- acute: severe abdominal pain out of proportion to physical findings, vomiting, bloody diarrhea, bloating, minimal peritoneal signs early in course, hypotension, shock, sepsis
- chronic: postprandial pain, fear of eating, weight loss
- common sites: superior mesenteric artery (SMA) supplied territory, “watershed” areas of colon – splenic flexure, left colon, sigmoid colon

Investigations

- labs: leukocytosis (non-specific), lactic acidosis (late finding)
 - amylase, LDH, CK, ALP can be used to observe progress
 - hypercoagulability workup if suspect venous thrombosis
- AXR: portal venous gas, intestinal pneumatosis, free air if perforation
- contrast CT: thickened bowel wall, luminal dilatation, SMA or SMV thrombus, mesenteric/portal venous gas, pneumatosis
- CT angiography is the gold standard for acute arterial ischemia

Treatment

- fluid resuscitation, NPO, prophylactic broad-spectrum antibiotics
- exploratory laparotomy
- angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, anticoagulation therapy
- segmental resection of necrotic intestine:
 - assess extent of viability; if extent of bowel viability is uncertain, a second look laparotomy 12-24 hrs later is mandatory



Pain “out of keeping with physical findings” is the hallmark of early intestinal ischemia.



An acute abdomen + metabolic acidosis is bowel ischemia until proven otherwise.

Appendix



Appendicitis

Epidemiology

- 6% of population, M>F
- 80% between 5-35 years of age

Pathogenesis

- luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess (walled off by omentum) or peritonitis
- etiology:
 - children or young adult: hyperplasia of lymphoid follicles, initiated by infection
 - adult: fibrosis/stricture, fecolith, obstructing neoplasm
 - other causes: parasites, foreign body

Clinical Features

- most reliable feature is progression of signs and symptoms
- low grade fever (38°C), rises if perforation
- abdominal pain then anorexia, nausea and vomiting
- classic pattern: pain initially periumbilical; constant, dull, poorly localized, then well localized pain over McBurney's point
 - due to progression of disease from visceral irritation (causing referred pain from structures of the embryonic midgut, including the appendix) to irritation of parietal structures
 - McBurney's sign

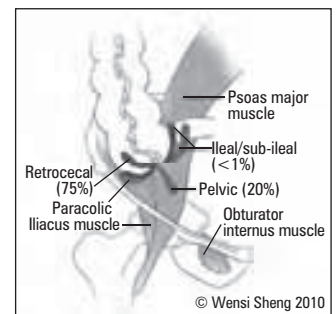


Figure 13. Appendix Anatomy



McBurney's Sign
Tenderness 1/3 the distance from the ASIS to the umbilicus on the right side.

Laparoscopic vs. Open Appendectomy**Laparoscopic Surgery**

- Intra-abdominal abscesses 3 times more likely
- Mean length of hospital stay reduced by 0.7 d
- Sooner return to normal activity, work and sport
- Costs outside hospital are reduced
- Reduced levels of pain on POD #1

Open Surgery

- Wound infections 2 times as likely
- Lower operation costs

Overview

Diagnostic laparoscopy led to a large reduction in the rate of negative appendectomies, and a reduction in surgeries with unestablished diagnosis. This was especially pronounced in fertile women due to a broader differential for appendicitis.

Sauerland S, Lefering R, Neugebauer EAM. Laparoscopic versus open surgery for suspected appendicitis (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Antibiotics versus Placebo for Prevention of Postoperative Infection after Appendectomy

Cochrane Database of Systematic Reviews 2005; 3

Study: Meta-analysis of Randomised Controlled Trials (RCTs) and Controlled Clinical Trials (CCTs), on both adults and children, in which any antibiotic regime was compared to placebo in patients undergoing appendectomy for suspected appendicitis.

Data Sources: Cochrane Central Register of Controlled Trials (2005 issue 1), PubMed (1966 to April 2005), EMBASE (1980 to April 2005), Cochrane Colorectal Cancer Group Specialised Register (April 2005), and reference lists from included studies.

Patients: Wound infection, 20 studies (n=2343). Postoperative Intra-abdominal abscess, 8 studies (n=1033).

Main Outcomes: (1) Wound infection (discharge of pus from the wounds) and (2) Postoperative intra-abdominal abscess (persistent pyrexia without any other focus, after operation, palpable mass in the abdomen or discharge of pus from the rectum).

Results: Treatment with antibiotics decreased infection rates with an NNT=37 ($p<0.00001$), while treatment with antibiotics decreased abscess rates with an NNT=199 ($p=0.03$).

Conclusion: Various prophylactic antibiotic regimens are effective in preventing postoperative complications. Further studies are required to determine the ideal regimen.

- signs:
 - inferior appendix: McBurney's sign (see above), Rovsing's sign (palpation pressure to left abdomen causes McBurney's point tenderness)
 - retrocecal appendix: psoas sign (pain on flexion of hip against resistance or passive hyperextension of hip)
 - pelvic appendix: obturator sign (flexion then external or internal rotation about right hip causes pain)
- complications:
 - perforation (especially if >24 hrs duration)
 - abscess, phlegmon

Investigations

- labs:
 - mild leukocytosis with left shift (may have normal WBC counts)
 - higher leukocyte count with perforation
 - beta-hCG to rule out ectopic pregnancy
 - urinalysis
- imaging:
 - upright CXR, AXR: usually nonspecific – free air if perforated (rarely), calcified fecolith, loss of psoas shadow
 - ultrasound: may visualize appendix, but also helps rule out gynecological causes – overall accuracy 90-94%
 - CT scan: thick wall, appendicolith, inflammatory changes – overall accuracy 94-100%, optimal investigation

Treatment

- hydrate, correct electrolyte abnormalities
- surgery + antibiotic coverage
- if localized abscess (palpable mass or large phlegmon on imaging and often pain >4-5 days), consider radiologic drainage + antibiotics x 14 d + interval appendectomy in 6 weeks
- appendectomy:
 - laparoscopic vs. open (see sidebar)
 - complications: spillage of bowel contents, pelvic abscess, enterocutaneous fistula
 - perioperative antibiotics:
 - ♦ ampicillin + gentamicin + metronidazole (antibiotics x 24 h only if non-perforated)
 - ♦ other choices: 2nd/3rd generation cephalosporin for aerobic gut organisms

Prognosis

- morbidity/mortality 0.6% if uncomplicated, 5% if perforated

Tumours of the Appendix

CARCINOID TUMOURS (most common type)

- see *Tumours of Small Intestines: Carcinoid*, GS21

ADENOCARCINOMA

- 50% present as acute appendicitis
- spreads rapidly to lymph nodes, ovaries, and peritoneal surfaces
- treatment: right hemicolectomy

OTHER

- malignant mucinous cystadenocarcinoma



Inflammatory Bowel Disease (IBD)

- see *Gastroenterology*, G19

Principles of Surgical Management

- can alleviate symptoms, address complications, improve quality of life
- conserve bowel – resect as little as possible to avoid short gut syndrome
- perioperative management:
 - optimize medical status: may require TPN (especially if >7 days NPO) and bowel rest
 - hold immunosuppressive therapy pre-op, provide pre-op stress dose of corticosteroid if patient had recent steroid therapy
 - deep vein thrombosis (DVT) prophylaxis: heparin (IBD patients at increased risk of thromboembolic events)

Crohn's Disease



Treatment

- surgery is NOT curative, but over lifetime ~70% of Crohn's patients will have surgery
- indications for surgical management:
 - failure of medical management
 - SBO (due to stricture/inflammation): indication in 50% of surgical cases
 - abscess, fistula (enterocolic, vesicular, vaginal, cutaneous abscess), quality of life, perforation, hemorrhage, chronic disability, failure to thrive (children), perianal disease
- surgical procedures:
 - resection and anastomosis/stoma if active or subacute inflammation, perforation, fistula
 - ♦ resection margin only has to be free of gross disease (microscopic disease irrelevant to prognosis)
 - stricturoplasty – widens lumen in chronically scarred bowel – relieves obstruction without resecting bowel (contraindicated in acute inflammation)



Crohn's 3 Major Patterns

- Ileocecal 40% (RLQ pain, fever, weight loss)
- Small intestine 30% (especially terminal ileum)
- Colon 25% (diarrhea)

Complications of Treatment

- short gut syndrome (diarrhea, steatorrhea, malnutrition)
- fistulas
- gallstones (if terminal ileum resected, decreased bile salt resorption → increased cholesterol precipitation)
- kidney stones (loss of calcium in diarrhea → increased oxalate absorption and hyperoxaluria → stones)



Findings in Crohn's

- "Cobblestoning" on mucosal surface due to edema and linear ulcerations
- "Skip lesions": normal mucosa in between
- "Creeping fat": mesentery infiltrated by fat
- Granulomas: 25-30%
- Barium enema: "lead-pipe appearance"

Prognosis

- recurrence rate at 10 years: ileocolic (25-50%), small bowel (50%), colonic (40-50%)
- re-operation at 5 years: primary resection (20%), bypass (50%), stricturoplasty (10% at 1 year)
- 80-85% of patients who need surgery lead normal lives
- mortality: 15% at 30 years

Ulcerative Colitis



Treatment

- indications for surgical management:
 - failure of medical management (including inability to taper steroids)
 - complications: hemorrhage, obstruction, perforation, toxic megacolon (emergency), failure to thrive (children)
 - reduce cancer risk (1-2% risk per year after 10 years of disease)
- surgical procedures:
 - proctocolectomy and ileal pouch-anal anastomosis (IPAA) ± rectal mucosectomy (operation of choice)
 - proctocolectomy with permanent end ileostomy (if not a candidate for ileoanal procedures)
 - colectomy and IPAA ± rectal mucosectomy
 - in emergency: total colectomy and ileostomy with Hartmann closure of the rectum, rectal preservation

Complications of Treatment

- early: bowel obstruction, transient urinary dysfunction, dehydration (high stoma output), anastomotic leak
- late: stricture, anal fistula/abscess, pouchitis, poor anorectal function, reduced fertility

Prognosis

- mortality: 5% over 10 years
- total proctocolectomy will completely eliminate risk of cancer
- perforation of the colon is the leading cause of death from ulcerative colitis



Diverticular Disease

Definitions

- diverticulum – abnormal sac or pouch protruding from the wall of a hollow organ
- diverticulosis – presence of multiple false diverticuli
- diverticulitis – inflammation of diverticuli
- right sided (true) diverticuli = contains all layers (congenital) (see Figure 14)
- left sided (false) diverticuli = contains only mucosal and submucosal layers (acquired)

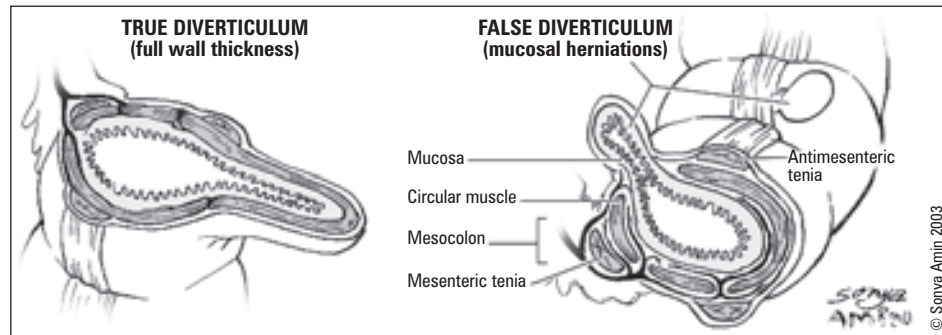


Figure 14. Diverticular Disease – Cross-Sections of True and False Diverticuli

Diverticulosis

Epidemiology

- 35-50% of general population, M=F
- increased incidence in 5th to 8th decades of life
- 95% involve sigmoid colon (site of highest pressure)
- higher incidence in Western countries, related to low fibre diet

Pathogenesis

- risk factors:
 - low-fibre diet (increases gut transit time and intraluminal pressure)
 - muscle wall weakness from aging and illness (e.g. Ehler-Danlos, Marfan's)
 - possible genetic component
- high intraluminal pressures cause outpouching to occur at area of greatest weakness: most commonly at the site of penetrating vessels at antimesenteric tenia, therefore increased risk of hemorrhage

Clinical Features

- uncomplicated diverticulosis: asymptomatic (70-80%)
- episodic LLQ abdominal pain, bloating, flatulence, constipation, diarrhea
- absence of fever/leukocytosis
- no physical exam findings or poorly localized LLQ tenderness
- complications:
 - diverticulitis (15-20%)
 - bleeding (5-15%): PAINLESS rectal bleeding, 2/3 of massive lower GI bleeds

Treatment

- uncomplicated diverticulosis: high fibre, education
- diverticular bleed:
 - initially work up and treat as any lower GI bleed
 - if hemorrhage does not stop, resect involved region

Diverticulitis ("left sided appendicitis")

Definition

- infection or perforation of a diverticulum

Pathogenesis

- erosion of the wall by increased intraluminal pressure (or inspissated food particles) → microperforation/macroporforation → inflammation and focal necrosis
- usually mild inflammation with perforation walled off by pericolic fat
- sigmoid colon most often involved

Clinical Features

- severity ranges from mild inflammation to feculent peritonitis
- LLQ pain/tenderness, present for several days before admission
- alternating constipation and diarrhea, urinary symptoms (dysuria if inflammation adjacent to bladder)
- palpable mass if phlegmon or abscess, nausea, vomiting
- low-grade fever, mild leukocytosis
- occult or gross blood in stool less common
- generalized tenderness suggests macroperforation and peritonitis
- complications:
 - abscess – on physical exam may find palpable abdominal mass
 - fistula – colovesical (most common), coloenteric, colovaginal, colocutaneous
 - obstruction – due to scarring from repeated inflammation
 - macroperforation → peritonitis (feculent vs. purulent)
 - ♦ recurrent attacks RARELY lead to peritonitis

Investigations

- AXR, upright CXR:
 - localized diverticulitis (ileus, thickened wall, SBO, partial colonic obstruction)
 - free air may be seen in 30% with perforation and generalized peritonitis
- CT scan (optimal method of investigation) :
 - 97% sensitive, very useful for assessment of severity and prognosis
 - very helpful in localizing an abscess
- Hypaque® (water soluble) enema – SAFE (under low pressure):
 - saw-tooth pattern (colonic spasm)
 - may show site of perforation, abscess cavities or sinus tracts, fistulas
- barium enema: contraindicated during an acute attack:
 - risk of chemical peritonitis (because of perforation)
- sigmoidoscopy/colonoscopy:
 - not during an acute attack, only done on an elective basis
 - take biopsies to rule out other diagnoses (polyps, malignancy)

Treatment

- admit, NPO, fluid resuscitation, NG + suction, IV antibiotics covering *B. fragilis* (e.g. ciprofloxacin, metronidazole)
- indications for surgery:
 - unstable patient with peritonitis
 - Hinchey stage 2-4 (see Table 10)
 - after 1 attack if: (a) immunosuppressed, (b) abscess needing percutaneous drainage
 - consider after 2 or more attacks, recent trend is toward conservative management of recurrent mild/moderate attacks
- complications: generalized peritonitis, free air, abscess fistula, obstruction, hemorrhage, inability to rule out colon cancer on endoscopy, or failure of medical management
- surgical procedures:
 - Hartmann procedure: resection + colostomy and rectal stump → colostomy reversal in 3-6 months (see Figure 15)
 - resection + primary anastomosis (± pre-op bowel prep or on-table lavage): controversial (anastomosis of inflamed tissues = increased risk of anastomotic leakage)

Prognosis

- 13-30% recurrence after 1st attack, 30-50% after 2nd attack

Table 10. Hinchey Staging and Treatment for Diverticulitis

Hinchey Stage	Description	Acute treatment
1	Phlegmon / small pericolic abscess	Medical
2	Large abscess / fistula	Abscess drainage, resection ± primary anastomosis
3	Purulent peritonitis (ruptured abscess)	Hartmann procedure, sometimes primary anastomosis
4	Feculent peritonitis	Hartmann procedure

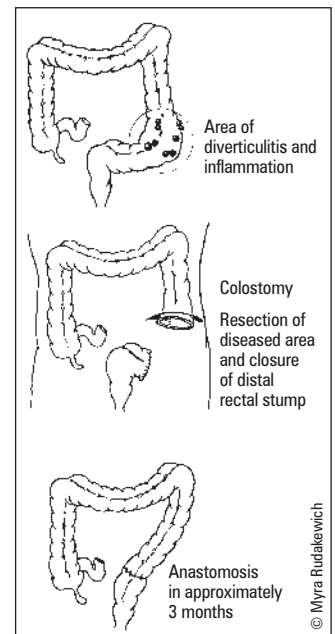


Figure 15. Hartmann Procedure

Colorectal Neoplasms

Colorectal Screening Guidelines

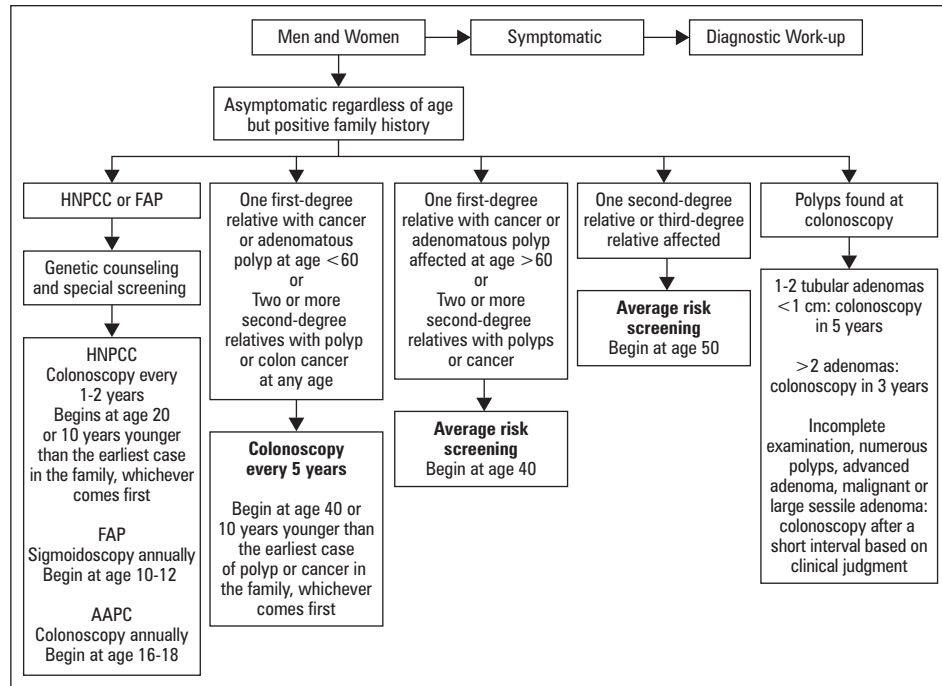


Figure 16. Approach to Higher Risk Screening

AAPC (attenuated adenomatous polyposis) FAP (familial adenomatous polyposis); HNPCC (hereditary nonpolyposis colorectal cancer); First degree relatives: parents, siblings, children; 2nd degree relatives: grandparents, aunts, uncles; 3rd degree relatives: great grandparents or cousins.

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Colorectal Polyps

Definition

- polyp: small mucosal outgrowth into the lumen of the colon or rectum
- sessile (flat) or pedunculated (on a stalk) (see Figure 17)

Epidemiology

- 30% of population have polyps by age 50, 40% by age 60, 50% by age 70

Table 11. Characteristics of Tubular vs. Villous Polyps

	Tubular	Villous
Incidence	Common (60% to 80%)	Less common (10%)
Size	Small (<2 cm)	Large (usually >2 cm)
Attachment	Pedunculated	Sessile
Malignant Potential	Lower	Higher
Distribution	Even	Left-sided predominance

Clinical Features

- 50% in the rectosigmoid region, 50% are multiple
- usually asymptomatic, but may have rectal bleeding, change in bowel habit, mucous per rectum
- usually detected during routine endoscopy or familial/high risk screening

Pathology

- non-neoplastic:
 - hyperplastic – most common non-neoplastic polyp
 - pseudopolyps – inflammatory, associated with IBD, no malignant potential

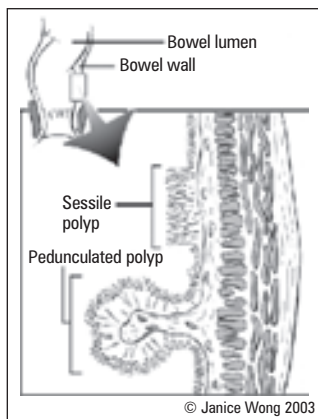


Figure 17. Sessile and Pedunculated Polyps

- neoplastic:
 - hamartomas: juvenile polyps (large bowel), Peutz-Jegher syndrome (small bowel)
 - ♦ malignant risk due to associated adenomas (large bowel)
 - ♦ low malignant potential → most spontaneously regress or autoamputate
 - adenomas – premalignant, often carcinoma in situ:
 - ♦ some may contain invasive carcinoma (“malignant polyp” – 3-9%): invasion into muscularis
 - ♦ malignant potential: villous > tubulovillous > tubular (see Table 11)

Investigations

- flexible sigmoidoscopy can reach 60% of polyps in men and 35% of polyps in women; if polyps detected, proceed to colonoscopy for examination of entire bowel and biopsy
- colonoscopy still the gold standard

Treatment

- indications: symptoms, malignancy or risk of malignancy (i.e. adenomatous polyps)
- endoscopic removal of entire growth
- surgical resection for those invading into muscularis (high risk of malignancy) and those too large to remove endoscopically
- follow-up endoscopy 1 year later, then every 3-5 years

Familial Colon Cancer Syndromes

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

Pathogenesis

- autosomal dominant (AD) inheritance, mutation in adenomatous polyposis coli (APC) gene on chromosome 5q

Clinical Features

- hundreds to thousands of colorectal adenomas usually by age 20 (by 40's in attenuated FAP)
- extracolonic manifestations:
 - carcinoma of duodenum, bile duct, pancreas, stomach, thyroid, adrenal, small bowel
 - congenital hypertrophy of retinal pigment epithelium presents early in life in 2/3 of patients
- virtually 100% lifetime risk of colon cancer (because of number of polyps)
- variants:
 - Gardner's syndrome: FAP + extraintestinal lesions (sebaceous cysts, osteomas, desmoid tumours)
 - Turcot's syndrome: FAP + CNS tumours (glioblastoma multiforme)

Investigations

- genetic testing (80-95% sensitive, 99-100% specific) (see sidebar)
- if no polyposis found: annual flexible sigmoidoscopy from puberty to age 50, then routine screening
- if polyposis found: annual colonoscopy and consider surgery (see Figure 16)

Treatment

- surgery indicated by age 17-20
- total proctocolectomy with ileostomy OR total colectomy with ileorectal anastomosis
- doxorubicin-based chemotherapy
- NSAIDs for intra-abdominal desmoids



Referral Criteria for Genetic Screening for APC

- To confirm the diagnosis of FAP (in patients with ≥100 colorectal adenomas)
- To provide pre-symptomatic testing for individuals at risk for FAP (1st degree relatives who are ≥10 years old)
- To confirm the diagnosis of attenuated FAP (in patients with ≥20 colorectal adenomas)

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC)

Pathogenesis

- AD inheritance, mutation in a DNA mismatch repair gene resulting in genomic instability and subsequent mutations

Clinical Features

- early age of onset, right > left colon, synchronous and metachronous lesions
- mean age of cancer presentation is 44 years, lifetime risk 70-80% (M>F)
 - Lynch syndrome I: hereditary site-specific colon cancer
 - Lynch syndrome II: cancer family syndrome – high rates of extracolonic tumours (endometrial, ovarian, hepatobiliary, small bowel)

Diagnosis

- diagnosis is clinical – based on Amsterdam Criteria:
 - at least 3 relatives with colorectal cancer or HNPCC related CA
 - 2 or more generations involved, and 1 must be 1st degree relative of the other 2
 - 1 case must be diagnosed before 50 years old
 - FAP is excluded



Revised Bethesda Criteria – Refer for Genetic Screening for HNPCC

- Individuals with cancer in families that meet the Amsterdam Criteria
- Patients with two HNPCC-related cancers, including synchronous and metachronous colorectal cancer or associated extracolonic cancers (endometrial, ovarian, gastric, hepatobiliary, small bowel, or transitional cell carcinoma of the renal pelvis or ureter).
- Patients with colorectal cancer and a first degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma with one of the cancers diagnosed before age 45, and the adenoma diagnosed before age 40.
- Patients with right-sided colorectal cancer having an undifferentiated pattern (solid/cirriiform) on histopathologic diagnosis before age 45.
- Patients with signet-ring cell type colorectal cancer diagnosed before age 45.
- Patients with adenomas diagnosed before age 40.



Screening for Colorectal Cancer (asymptomatic, no history of UC, polyps, or CRC)

- Average risk individuals, at age 50 (incl. those with <2 relatives with CRC) – recommendations are variable:
 - American Gastroenterology Society and American Cancer Society
 - Yearly fecal occult blood test (FOBT), flexible sigmoidoscopy q5y, colonoscopy q10y
 - Canadian Task Force on Preventative Health Care:
 - Yearly FOBT (“A” recommendation)
 - Sigmoidoscopy (“B” recommendation)
 - Whether to use one or both of FOBT or sigmoidoscopy (“C” recommendation)
 - Colonoscopy (“C” recommendation due to lack of good RCTs)
- Family Hx (>2 relatives with CRC/adenoma, one being a 1st degree relative):
 - Start screening 10 years prior to the age of the relative's with the earliest onset of carcinoma
- FAP genetic testing +ve:
 - Yearly sigmoidoscopy starting at puberty (“B” recommendation)
- HNPCC genetic testing +ve:
 - Yearly colonoscopy starting at age 20 (“B” recommendation)



Elderly persons who present with iron-deficiency anemia should be investigated for colon cancer.

Investigations

- genetic testing (80% sensitive) – colonoscopy mandatory even if negative
 - refer for genetic screening individuals who fulfill EITHER the Amsterdam Criteria (as above) OR the revised Bethesda Criteria (see sidebar)
- colonoscopy (starting age 20) annually
- surveillance for extracolonic lesions

Treatment

- total colectomy and ileorectal anastomosis with yearly proctoscopy

Colorectal Carcinoma (CRC)



Epidemiology

- 3rd most common cancer (after lung, prostate/breast), 2nd most common cause of cancer death

Risk Factors

- most patients have no specific risk factors
- FAP, HNPCC, family history of CRC
- adenomatous polyps (especially if >1 cm, villous, multiple)
- age >50 (dominant risk factor in sporadic cases), mean age is 70
- IBD (especially UC: risk is 1-2%/yr if UC >10 yrs)
- previous colorectal cancer (also gonadal or breast)
- diet (increased fat, red meat, decreased fibre) and smoking
- diabetes mellitus (insulin is a growth factor for colonic mucosal cells) and acromegaly

Screening Tools

- digital rectal exam (DRE): most common exam, but not recommended as a screening tool
- fecal occult blood test (FOBT):
 - proper test requires 3 samples of stool collected at 3 different times
 - recommended annually by the World Health Organization (WHO)
 - results in 16-33% reduction in mortality in RCTs
 - Minnesota Colon Cancer Study: RCT showed that annual FOBT can decrease mortality rate by 1/3 in patients 50-80 years old
- sigmoidoscopy:
 - can identify 30-60% of lesions
 - sigmoidoscopy + FOBT misses 24% of colonic neoplasms
- colonoscopy:
 - can remove or biopsy lesions during procedure
 - can identify proximal lesions missed by sigmoidoscopy
 - used as follow-up to other tests if lesions found
 - disadvantages: expensive, not always available, poor compliance, requires sedation, risk of perforation (0.2%)
- virtual colonoscopy (CT colonography): 91% sensitive, 17% false positive rate
- air contrast barium enema (ACBE): 50% sensitive for large (>1 cm) adenomas, 39% for polyps

Pathogenesis

- adenoma-carcinoma sequence; rarely arise *de novo*

Clinical Features (see Table 12)

- often asymptomatic
- hematochezia/melena, abdominal pain, change in bowel habits
- others: weakness, anemia, weight loss, palpable mass, obstruction
- 3-5% have synchronous lesions
- spread:
 - direct extension, lymphatic, hematogenous (liver most common, lung, rarely bone and brain)
 - peritoneal seeding: ovary, Blumer's shelf (pelvic cul-de-sac)
 - intraluminal

Table 12. Clinical Presentation of CRC

	Right Colon	Left Colon	Rectum
Frequency	25%	35%	30%
Pathology	Exophytic lesions with occult bleeding	Annular, invasive lesions	Ulcerating
Symptoms	Weight loss, weakness, rarely obstruction	Constipation ± overflow (alternating bowel patterns), abdominal pain, decreased stool caliber, rectal bleeding	Obstruction, tenesmus, rectal bleeding
Signs	Fe-deficiency anemia, RLQ mass (10%)	BRBPR, LBO	Palpable mass on DRE, BRBPR

Investigations

- colonoscopy (best), look for synchronous lesions; alternative: air contrast barium enema ("apple core" lesion) + sigmoidoscopy
- if a patient is FOBT +ve, has microcytic anemia or has a change in bowel habits, do colonoscopy
- metastatic workup: CXR, abdominal CT/ultrasound
- bone scan, CT head only if lesions suspected
- labs: CBC, urinalysis, liver function tests, CEA (before surgery for baseline)
- staging (see Table 13 and sidebar)
- rectal cancer: pelvic MRI or endorectal ultrasound to determine T and N stage

Table 13. TNM Classification System for Staging of Colorectal Carcinoma

Primary Tumour (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
T0 No primary tumour found	N0 No regional node involvement	M0 No distant metastasis
Tis Carcinoma in situ	N1 Metastasis in 1-3 pericolic nodes	M1 Distant metastasis
T1 Invasion into submucosa	N2 Metastasis in 4 or more pericolic nodes	
T2 Invasion into muscularis propria	N3 Metastasis in any nodes along the course of named vascular trunks	
T3 Invasion through muscularis and into serosa		
T4 Invasion into adjacent structures or organs		

Treatment

- surgery (indicated in potentially curable or symptomatic cases – not usually in stage IV)
 - curative: wide resection of lesion (5 cm margins) with nodes and mesentery
 - palliative: if distant spread, then local control for hemorrhage or obstruction
 - 80% of recurrences occur within 2 years of resection
 - improved survival if metastasis consists of solitary hepatic mass that is resected
 - colectomy:
 - ♦ most patients get primary anastomosis [e.g. hemicolectomy, low anterior resection (LAR)] (see Figure 18)
 - ♦ if cancer is low in rectum, patient may require an abdominal perineal resection (APR) with a permanent end colostomy, especially if lesion involves the sphincter complex
 - ♦ complications: anastomotic leak or stricture, recurrent disease, pelvic abscess, enterocutaneous fistula
- radiotherapy and chemotherapy:
 - chemotherapy (5-FU based regimens): for patients with node-positive disease
 - radiation: for patients with node-positive or transmural rectal cancer (pre ± post-op), not effective as 1^o treatment of colon cancer
 - adjuvant therapy: chemotherapy (colon) and radiation (rectum)
 - palliative chemotherapy/radiation therapy for improvement in symptoms and survival
 - neoadjuvant chemoradiation for T3 or N1 rectal cancer

Case Finding for Colorectal Cancer (symptomatic or history of UC, polyps, or CRC)

- surveillance (when polyps are found): colonoscopy within 3 years after initial finding
- patients with past CRC: colonoscopy every 3-5 years, or more frequently
- IBD: some recommend colonoscopy every 1-2 years after 8 years of disease (especially UC)

Follow-Up

- intensive follow up improves overall survival in low risk patients
- currently there are no data suggesting optimal follow-up
- combination of periodic CT chest/abdo/pelvis, CEA and colonoscopy is recommended
- carcinogenic embryonic antigen (CEA): to monitor for initial response to treatment, and to assess for recurrence q3 months (not a screening test)



Staging for CRC

- I T1,2 N0M0
- II T3,4 N0M0
- III TxN+M0
- IV TxNxM1



Prognosis for CRC

Stage	5 yr survival %
T ₁ N ₀ M ₀	>90
T ₂ N ₀ M ₀	85
T ₃ N ₀ M ₀	70-80
T _x N ₁ M ₀	35-65
T _x N _x M ₁	5

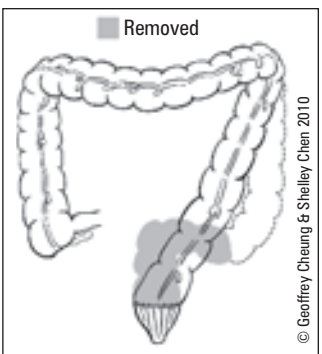


Figure 18. Low Anterior Resection (LAR)

Combined-modality Treatment for Resectable Metastatic Colorectal Cancer to the Liver: Surgical Resection of Hepatic Metastases in Combination with Continuous Infusion of Chemotherapy – An Intergroup Study

J Clin Oncol 2002; 20(6):1499-505

Background: Metastatic spread of colorectal cancer commonly targets the liver, and long-term outcome studies of surgical resection of hepatic metastases have shown high rates of treatment failure. Arterial chemotherapy regimens targeted to the liver represent a promising adjuvant treatment to reduce recurrence rates.

Methods: Patients with 1-3 resectable liver metastases were randomized preoperatively to receive no further intervention (45 patients, control group) or postoperative floxuridine and fluorouracil (30 patients).

Results: 4-year recurrence-free survival rates were 25% for the control group and 46% for the chemotherapy group ($P=0.04$), with liver recurrence-free rates of 43% and 67% respectively ($P=0.03$).

Conclusions: Adjuvant intra-arterial and intravenous chemotherapy shows promise in preventing hepatic recurrence after surgical resection of colorectal cancer hepatic metastases.



APR removes distal sigmoid colon, rectum and anus, permanent end colostomy required.

LAR removes distal sigmoid and rectum with anastomosis of distal colon to anus.

Other Conditions of the Large Intestine

Angiodysplasia

Definition

- vascular anomaly: focal submucosal venous dilatation and tortuosity

Clinical Features

- most frequently in right colon of patients >60 years old
- bleeding typically intermittent (melena, anemia, guaiac positive stools)

Investigations

- endoscopy (cherry red spots, branching pattern from central vessel)
- angiography (slow filling/early emptying mesenteric vein, vascular tuft)
- RBC technetium-99 scan
- barium enema is contraindicated (obscures other x-rays, i.e. angiogram)

Treatment

- none if asymptomatic
- cautery, right hemicolectomy, embolization, vasopressin infusion, sclerotherapy, band ligation, laser, octreotide, and rarely segmental resection if other treatments fail

Volvulus

Definition

- rotation of segment of bowel about its mesenteric axis
- sigmoid (70%), cecum (30%)

Risk Factors

- age (50% of patients >70 yrs: stretching/elongation of bowel with age is a predisposing factor)
- high fibre diet (can cause elongated/redundant colon), chronic constipation, laxative abuse, pregnancy, bedridden, institutionalized (less frequent evacuation of bowels)
- congenitally hypermobile cecum

Clinical Features

- symptoms due to bowel obstruction (GS23) or intestinal ischemia (GS27)

Investigations

- AXR: "omega", "bent inner-tube", "coffee-bean" signs (see sidebar)
- barium/gastrografin enema: "ace of spades" (or "bird's beak") appearance due to funnel-like luminal tapering of lower segment towards volvulus
- sigmoidoscopy or colonoscopy as appropriate
- CT

Treatment

- initial supportive management with fluid, electrolyte resuscitation
- cecum:
 - nonsurgical
 - ♦ may attempt colonoscopic detorsion and decompression
 - surgical:
 - ♦ right colectomy + ileotransverse colonic anastomosis
- sigmoid:
 - nonsurgical
 - ♦ decompression by flexible sigmoidoscopy and insertion of rectal tube past obstruction
 - ♦ subsequent elective surgery recommended (50-70% recurrence)
 - surgical: Hartmann procedure (if urgent)
 - ♦ indications: strangulation, perforation or unsuccessful endoscopic decompression



Cecal Volvulus

AXR: Central cleft of "coffee bean" sign points to RLQ.



Sigmoid Volvulus

AXR: Central cleft of "coffee bean" sign points to LLQ.

Barium enema: "ace of spades" or "bird's beak" sign.



Gastric Volvulus

Brochard's Triad

Epigastric distention

Failure to pass NG tube

Emesis followed by inability to vomit

Treatment: exploratory laparotomy to untwist and gastropexy

Fistula

Definition

- abnormal communication between two epithelialized surfaces (e.g. enterocutaneous, colovesical, aortoenteric, entero-enteric)

Etiology

- foreign object erosion (e.g. gallstone, graft)
- infection, IBD (especially Crohn's), diverticular disease
- iatrogenic/surgery (e.g. postoperative anastomotic leak)
- congenital, trauma
- neoplastic

Investigations

- contrast radiography (fistulogram)
- sonogram
- CT scan
- measure amount of drainage from fistula

Treatment

- fluid resuscitation, manage electrolytes
- bowel rest – NPO
- drain any abscesses/control sepsis
- nutrition – elemental/low residue, TPN
- decrease secretion – octreotide/somatostatin/omeprazole
- skin care (for enterocutaneous fistula)
- surgical intervention – dependent upon etiology (for non-closing fistulas); uncertainty of diagnosis



Why Fistulae Stay Open

FRIENDO

- Foreign body
- Radiation
- Infection
- Epithelialization
- Neoplasm
- Distal obstruction (most common)
- Others: increased flow; steroids (may inhibit closure, usually will not maintain fistula)

Ostomies

Definition

- an opening of the GI tract onto the surface of the abdomen wall
- types (see Figure 19): colostomy vs. ileostomy, temporary vs. permanent, continent vs. incontinent, end vs. loop, ileoconduit
 - end (Brooke) ileostomy: for incontinent, continuous drainage in patients requiring total colectomy
 - Koch ileostomy: for continent, manual drainage – rarely used

Complications (10%)

- obstruction: herniation, stenosis (skin and abdominal wall), adhesive bands, volvulus
- peri-ileostomy abscess and fistula
- skin irritation
- prolapse or retraction
- diarrhea (excessive output)



Colostomy/Ileostomy

- Connection of proximal limb of colon or ileum to abdominal wall skin

Mucous Fistula

- Connection of distal limb of colon to abdominal wall skin

Ileoconduit

- Connection of colon to ureter proximally + abdominal wall distally to drain urine

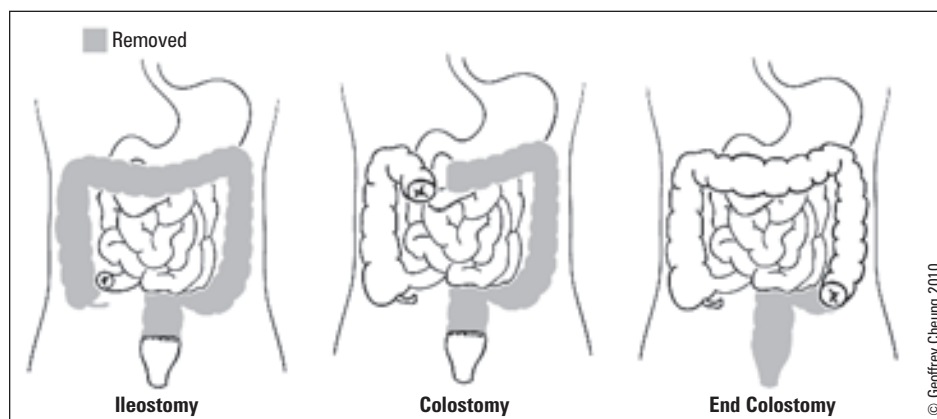


Figure 19. Ostomies

Anorectum

Hemorrhoids



Always rule out more serious causes (e.g. colon CA) in a person with hemorrhoids and rectal bleeding.

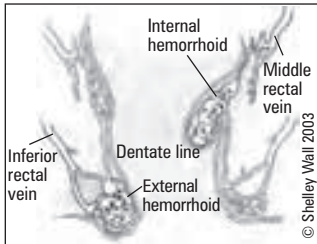


Figure 20. Hemorrhoids

Etiology

- vascular and connective tissue complexes form a plexus of dilated veins (cushion)
 - internal: superior hemorrhoidal veins, above dentate line, portal circulation
 - external: inferior hemorrhoidal veins, below dentate line, systemic circulation

Risk Factors

- increased intra-abdominal pressure: chronic constipation, pregnancy, obesity, portal hypertension, heavy lifting

Clinical Features and Treatment

- internal hemorrhoids (see Figure 20):
 - engorged vascular cushions usually at 3, 7, 11 o'clock positions (patient in lithotomy position)
 - painless rectal bleeding, anemia, prolapse, mucus discharge, pruritus, burning pain, rectal fullness:
 - 1st degree:** bleed but do not prolapse through the anus
 - treatment: high fibre/bulk diet, sitz baths, steroid cream, pargoline (Anusol®), rubber band ligation, sclerotherapy, photocoagulation
 - 2nd degree:** prolapse with straining, spontaneous reduction
 - treatment: rubber band ligation, photocoagulation
 - 3rd degree:** prolapse requiring manual reduction
 - treatment: same as 2nd degree, but may require closed hemorrhoidectomy
 - 4th degree:** permanently prolapsed, cannot be manually reduced
 - treatment: closed hemorrhoidectomy
- external hemorrhoids (see Figure 20):
 - dilated venules usually mildly symptomatic
 - pain after bowel movement, associated with poor hygiene
 - medical treatment: dietary fibre, stool softeners, steroid cream (short course), pargoline (Anusol®), avoid prolonged straining
 - thrombosed hemorrhoids are very painful:
 - resolve within 2 weeks, may leave excess skin = perianal skin tag
 - treatment: consider surgical decompression within first 48 hours of thrombosis, otherwise medical treatment

Anal Fissures

Definition

- tear of anal canal below dentate line (very sensitive squamous epithelium)
- 90% posterior midline, 10% anterior midline
- if off midline: consider IBD, STIs, TB, leukemia or anal carcinoma
- repetitive injury cycle after first tear:
 - sphincter spasm occurs preventing edges from healing and leads to further tearing
 - ischemia may ensue and contribute to chronicity

Etiology

- large, hard stools and irritant diarrheal stools
- tightening of anal canal secondary to nervousness/pain
- others: habitual use of cathartics, childbirth

Clinical Features

- acute fissure:
 - very painful bright red bleeding especially after bowel movement
 - treatment is conservative: stool softeners, sitz baths
- chronic fissure:
 - triad: fissure, sentinel skin tags, hypertrophied papillae
 - treatment:
 - stool softeners, bulking agents, sitz baths
 - topical nitroglycerin or nifedipine – increases local blood flow, promoting healing and relieves sphincter spasm
 - surgery (most effective) – lateral internal sphincterotomy; objective is to relieve sphincter spasm → increases blood flow and promotes healing; but 5% chance of fecal incontinence therefore not commonly done
 - alternative treatment:
 - botulinum toxin – inhibits release of acetylcholine (ACh), reducing sphincter spasm

Anorectal Abscess

Definition

- infection in one or more of the anal spaces (see Figure 21)
- usually bacterial infection of blocked anal gland at the dentate line
 - E. coli*, *Proteus*, *Streptococci*, *Staphylococci*, *Bacteroides*, anaerobes

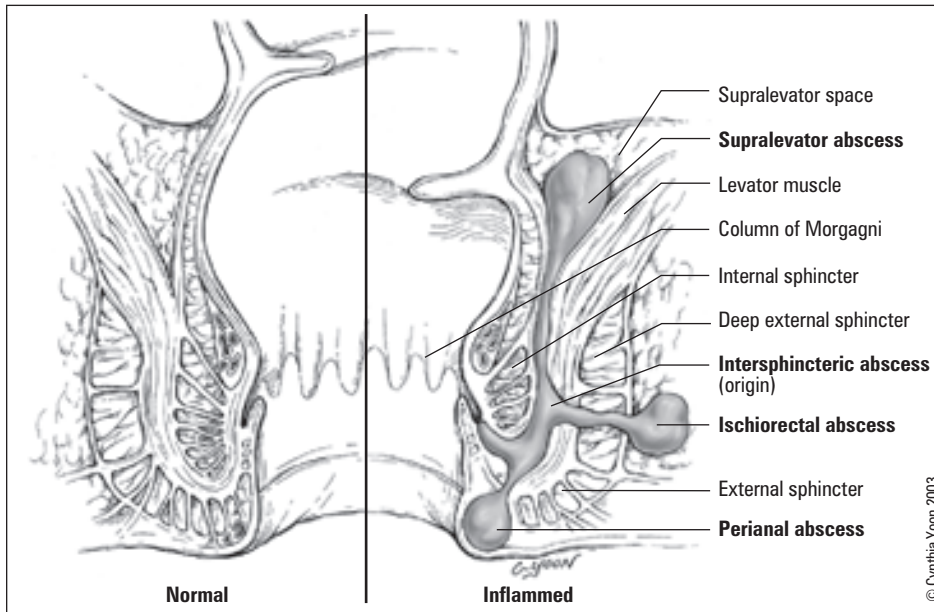


Figure 21. Different Types of Perianal Abscesses

Clinical Features

- throbbing pain that may worsen with straining and ambulation
- abscess can spread vertically downward (perianal), vertically upward (supralelevator) or horizontally (ischiorectal)
- tender perianal/rectal mass on exam

Treatment

- incision and drainage
 - curative in 50% of cases
 - 50% develop anorectal fistulas
- may require antibiotics if diabetic, heart murmur or cellulitis

Fistula-In-Ano

Definition

- connection between two epithelialized surfaces, one must be the rectum or anus
- an inflammatory tract with internal os at dentate line, external os on skin

Etiology

- see *Fistula*, GS37
- same perirectal process as anal abscess therefore usually associated with abscess
- other causes: post-op, trauma, anal fissure, malignancy, radiation proctitis

Clinical Features

- intermittent or constant purulent discharge from perianal opening
- pain
- palpable cord-like tract

Treatment

- identification:
 - internal opening:
 - Goodsall's rule (see Figure 22):
 - a fistula with an external opening anterior to the transverse anal line will have its internal opening at relatively the same position (e.g. external opening at 2 o'clock = internal opening at 2 o'clock) whereas all external openings posterior to the line will tend to have their internal openings in the midline
 - fistulous tract:
 - probing or fistulography under anesthesia

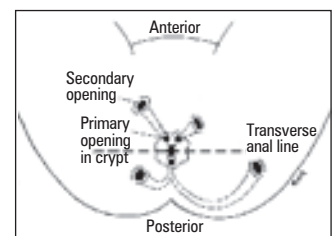


Figure 22. Goodsall's Rule

- surgery:
 - fistulotomy: unroof tract from external to internal opening, allow drainage
 - low lying fistula (does not involve external sphincter) → primary fistulotomy
 - high lying fistula (involves external sphincter) → staged fistulotomy with Seton suture placed through tract:
 - ♦ promotes drainage
 - ♦ promotes fibrosis and decreases incidence of incontinence
 - ♦ delineates anatomy
 - ♦ usually done to spare muscle cutting

Postoperative

- sitz baths, irrigation and packing to ensure healing proceeds from inside to outside

Complications

- recurrence
- rarely fecal incontinence

Pilonidal Disease

Definition

- acute abscess or chronic draining sinus in sacrococcygeal area

Epidemiology

- occurs most frequently in young men age 15-40 yrs

Etiology

- obstruction of the hair follicles in this area → formation of cysts, sinuses or abscesses

Clinical Features

- asymptomatic until acutely infected, then pain/tenderness, purulent discharge

Treatment

- acute abscess:
 - incision and drainage
 - wound packed open
 - 40% develop chronic pilonidal sinuses
- chronic disease:
 - pilonidal cystotomy
 - excision of sinus tract and cyst ± marsupialization (cyst edge sewn to surrounding tissue to leave sinus tract open)

Rectal Prolapse

Definition

- protrusion of full thickness of rectum through anus

Epidemiology

- extremes of ages – <5 years old and >5th decade
- 85% women

Etiology

- lengthened attachment of rectum secondary to constant straining
- 3 types:
 - I – false/mucosal: redundant rectal mucosa, radial furrows
 - II – incomplete: rectal intussusception without sliding hernia
 - III – true/complete (most common) (see Figure 23):
 - ♦ protrusion of entire rectal wall through anal orifice with herniation of pelvic peritoneum/cul-de-sac
 - ♦ circular furrows

Risk Factors

- gynecological surgery
- chronic neurologic/psychiatric disorders affecting motility

Clinical Features

- extrusion of mass with increased intra-abdominal pressure:
 - straining, coughing, laughing, Valsalva
- difficulty in bowel regulation:
 - tenesmus, constipation, fecal incontinence
- permanently extruded rectum with excoriation, ulceration and constant soiling
- may be associated with urinary incontinence or uterine prolapse

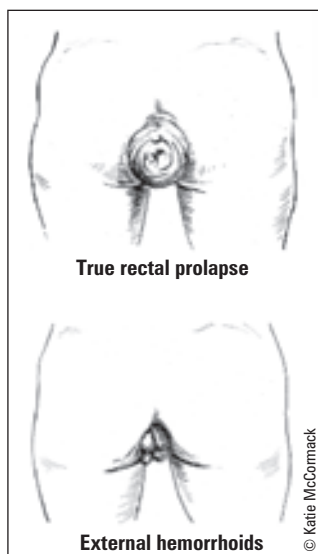


Figure 23. Rectal Prolapse (true vs. false)

Treatment

- Types I and II (false/mucosal/incomplete):
 - conservative – gentle replacement of prolapsed area, especially in children
 - hemorrhoidectomy with excision of redundant mucosa, mostly in adults
- Type III (true/complete):
 - conservative – reduce if possible
 - surgery – abdominal, perineal, transsacral approaches

Anal Neoplasms

ANAL CANAL**Squamous Cell Carcinoma (SCC) of Anal Canal (above dentate line)**

- most common tumour of anal canal (75%)
- anus prone to human papilloma virus (HPV) infection, therefore at risk for anal squamous intraepithelial lesions (ASIL)
 - high grade squamous intraepithelial lesion (HSIL) and low grade squamous intraepithelial lesion (LSIL) terminology used
- clinical features: anal pain, bleeding, mass, ulceration
- treatment: chemotherapy \pm radiation \pm surgery
- prognosis: 80% 5-year survival

Malignant Melanoma (MM) of Anal Canal

- 3rd most common site for primary MM after skin, eyes
- aggressive, distant metastases common at time of diagnosis
- treatment: early radical surgery
- prognosis: <5% 5-year survival

ANAL MARGIN

- clinical features and treatment as for skin tumours elsewhere
- squamous and basal cell carcinoma, Bowen's disease (SCC in situ) and Paget's disease

Liver

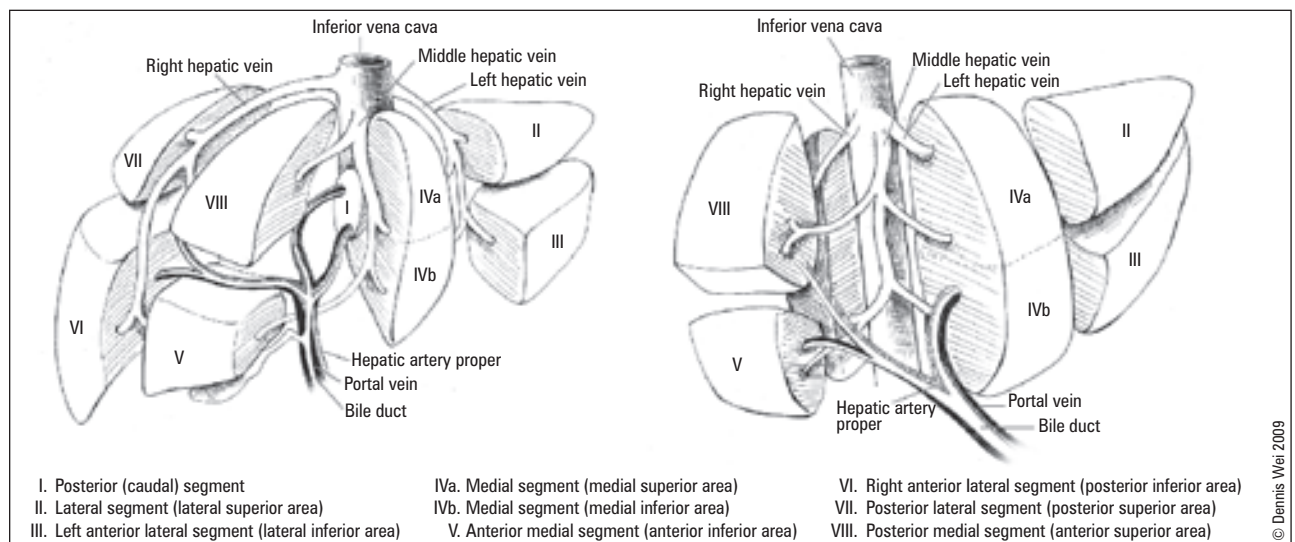


Figure 24. Segmental Anatomy of Liver

Liver Cysts

SIMPLE CYSTS

- most common type of liver cyst, may have multiple simple cysts
- clinical features: usually asymptomatic, if large may present with pain or mass
- treatment: generally not required for simple cysts unless very large
- complications: intracystic hemorrhage (may be confused with complex cysts)

POLYCYSTIC LIVER DISEASE

- progressive condition where cysts replace much of the liver
- 50% associated with polycystic kidney disease
- treatment: if symptomatic treat by partial liver resection or by creating drainage for cysts

CHOLEDOCHAL CYSTS

- congenital malformations of pancreaticobiliary tree
- 4 types, most extreme form called Caroli's disease (multiple cystic dilations in intrahepatic ducts)
- clinical features: recurrent abdominal pain, intermittent jaundice, RUQ mass
- diagnosis: U/S, transhepatic cholangiography, LFTs
- treatment:
 - high risk of malignancy, current treatment is complete excision of cysts
 - extent of resection depends on type of cyst
 - liver transplant indicated if cyst involves intrahepatic bile ducts (Caroli's disease)
- complications of chronic choledochal cysts: biliary cirrhosis, portal hypertension, cholangiocarcinoma

HYDATID LIVER CYSTS (CYSTIC ECHINOCOCCOSIS)

- etiology:
 - infection with parasite *Echinococcus granulosus*
 - endemic to Southern Europe, Middle East, Australasia, South America
 - associated with exposure to dogs, sheep and cattle
- clinical features:
 - asymptomatic mass (most often) or chronic pain, hepatomegaly
 - rupture can cause biliary colic, jaundice or anaphylactic reaction
- investigations:
 - detection of anti-Echinococcus Ab (IgG) using ELISA or RIA
 - U/S, CT: presence of mass, often calcified
 - DO NOT perform needle biopsy as can cause seeding of abdominal cavity or anaphylaxis
- treatment:
 - medical: albendazole (anti-helminthic) – cure up to 30%
 - surgical (risk of spillage into abdomen):
 - ♦ conservative – open endocystectomy ± omentoplasty
 - ♦ radical – partial hepatectomy or total pericystectomy

CYSTADENOMA (PREMALIGNANT)/CYSTADENOCARCINOMA

- clinical features:
 - appear as complex cysts on imaging: internal septae, papillary projections, irregular lining
- all complex, multiloculated cysts (except echinococcal) should be excised because of malignancy risk

Liver Abscesses

Etiology

- types:
 - pyogenic (bacterial): most often Gram-negatives – *E. coli*, *Klebsiella*, *Proteus*
 - parasitic (amoebic): *Entamoeba histolytica*
 - fungal
- sources: direct spread from biliary tract infection, portal spread from GI infection, systemic infection (e.g. endocarditis)

Clinical Features

- fever, malaise, chills, anorexia, weight loss, abdominal pain, nausea
- RUQ tenderness, hepatomegaly, jaundice, dullness to percussion

Investigations

- leukocytosis, anemia, elevated liver enzymes, hemagglutination titres for *Entamoeba* antibodies
- U/S, CXR (right basilar atelectasis/effusion), CT

Treatment

- treat underlying cause
- surgical or percutaneous drainage and IV antibiotics

Prognosis

- overall mortality 15% – higher rate if delay in diagnosis, multiple abscesses, malnutrition

Neoplasms

BENIGN LIVER NEOPLASMS**Hemangioma (cavernous)**

- pathogenesis: most common benign hepatic tumour; results from malformation of angioblastic fetal tissue
- risk factors: F:M = 6:1, steroid therapy, estrogen (exogenous, pregnancy)
- clinical features:
 - usually small and asymptomatic, larger tumours may produce pain or compress nearby structures
 - shock if ruptured (very rare)

- investigations:
 - contrast CT (well-demarcated hypodense mass with peripheral enhancement and delayed venous emptying), U/S (homogenous hyperechoic mass), arteriography (rarely used; "cotton wool" appearance), RBC scan
 - biopsy may result in hemorrhage
- treatment:
 - usually none unless tumour bleeds or is symptomatic, then excision by lobectomy or enucleation

Adenoma

- definition: benign glandular epithelial tumour
- risk factors: female, age 30-50, estrogen (OCP, pregnancy)
- clinical features: asymptomatic, 25% present with RUQ pain or mass
- investigations: CT (well-demarcated masses, often heterogenous, isodense on non-contrast CT, peripheral enhancement/isodense/hypodense on contrast CT), U/S (variable appearance; usually hyperechoic), biopsy
- treatment:
 - stop anabolic steroids or OCP
 - excise, especially if large (>5 cm), due to risk of malignancy and spontaneous rupture/hemorrhage

Focal Nodular Hyperplasia

- pathogenesis: thought to be due to local ischemia and tissue regeneration
- risk factors: female, middle age
- clinical features: asymptomatic, rarely grows or bleeds, no malignant potential
- investigations: central stellate scar on CT scan, technetium-99 scan is helpful
- treatment: may be difficult to distinguish from adenoma (malignant potential) → often resected

MALIGNANT LIVER NEOPLASMS

Primary

- usually hepatocellular carcinoma (HCC)/hepatoma
- others include angiosarcoma, hepatoblastoma, hemangioendothelioma
- epidemiology: uncommon in North America, but represents 20-25% of all carcinomas in Asia and Africa
- risk factors:
 - chronic liver inflammation: chronic hepatitis B (inherently oncogenic) and C, cirrhosis (especially macronodular), hemochromatosis, α_1 -anti-trypsin
 - meds: OCPs (3x increased risk), steroids
 - smoking, alcohol
 - chemical carcinogens (aflatoxin, vinyl chloride – associated with angiosarcoma)
- clinical features:
 - RUQ discomfort, right shoulder pain
 - jaundice, weakness, weight loss, \pm fever
 - hepatomegaly, bruit, rub
 - ascites with blood (sudden intra-abdominal hemorrhage)
 - paraneoplastic syndromes – e.g. Cushing's syndrome, hypoglycemia
 - metastasis: lung, bone, brain, peritoneal seeding
- investigations:
 - elevated ALP, bilirubin, and α -fetoprotein (80% of patients)
 - U/S (poorly-defined margins with internal echos), triphasic CT (enhancement on arterial phase and washout on portal venous phase), MRI, CT or MRI angiography
 - biopsy
- treatment:
 - cirrhosis is a *relative* contraindication to tumour resection due to decreased hepatic reserve
 - surgical: resection (10% of patients have resectable tumours)
 - liver transplant (if cirrhosis plus solitary nodule <5 cm, or less than 3 nodules each <3 cm (Milan criteria); generally not with extrahepatic disease or vascular invasion)
 - non-surgical: radiofrequency ablation, percutaneous ethanol injection, transcatheter arterial chemoembolization (TACE), chemotherapy (limited efficacy)
- prognosis:
 - 70% have metastases to nodes and lung
 - survival without treatment: 3 months
 - 5 year survival: all patients – 5%; patients undergoing complete resection – 11-40%

Secondary

- most common hepatic malignancy
- etiology:
 - GI (most common), lung, breast, pancreas, ovary, uterus, kidney, gallbladder, prostate
- treatment:
 - hepatic resection if control of primary is possible, no extrahepatic or extrapulmonary metastases and if possibility of "curative" resection
 - possible chemotherapy
- prognosis: 30-40% 5-year survival with a "curative" resection; prognosis same if metastases are multilobar compared with confined to one lobe



Differential Diagnosis of Metastatic Liver Mass

Some GU Cancers Produce Bumpy Lumps:
 Stomach
 Genitourinary cancers – kidney, ovary, uterus
 Colon
 Pancreas
 Breast
 Lung



Child-Turcotte-Pugh Score (Prognosis of Chronic Liver Disease/Cirrhosis, Including Postoperatively)

	1 Point	2 Points	3 Points
Albumin	>35 >3.5 g/dL	30-35 3.0-3.5	<28 <3.0
Ascites	Absent	Easily controlled	Poorly controlled
Bilirubin	<34 umol/L <2.0 mg/dL	34-51 2.0-3.0	>51 >3.0
Coagulation (INR)	<1.7 PT 0-4s	1.7-2.3 4-6	>2.3 >6
Hepatic encephalopathy	None	Minimal (Grade I-II)	Advanced (Grade III-IV)

Points	Class	One Year Survival	Two Year Survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Liver Transplantation

Table 14. Conditions Leading to Transplantation

Parenchymal Disease	Cholestatic Disease	Inborn Errors	Tumours
Chronic hepatitis B or C*	Biliary atresia**	α_1 -anti-trypsin deficiency	Hepatoma
Alcoholic cirrhosis	Primary biliary cirrhosis	Wilson's disease	
Acute liver failure	Sclerosing cholangitis	Hemochromatosis	
Budd-Chiari syndrome			
Congenital hepatic fibrosis			
Cystic fibrosis (CF)			

*leading cause in adults; ** leading cause in children

Clinical Indications

- early referral for transplant should be considered for all patients with progressive liver disease not responding to medical therapy, especially decompensated cirrhosis, unresectable primary liver cancers and fulminant hepatic failure
- end-stage liver disease with life expectancy <1 year and if no other therapy is appropriate
- progressive jaundice, refractory ascites, spontaneous hepatic encephalopathy, recurrent sepsis, fulminant hepatic failure
- recurrent variceal hemorrhage, coagulopathy, severe fatigue

Criteria for Transplantation

- Model for End-Stage Liver Disease (MELD): considers probability of death within 3 months if patient does not receive transplant; based on creatinine, bilirubin, INR
- Child-Turcotte-Pugh Score: patient must have ≥ 7 points (Class B)

Contraindications

- sepsis, HIV positive status
- active alcohol/substance abuse
- extrahepatic metastasis
- advanced cardiopulmonary disease

Post-op Complications

- primary non-function (graft failure) – urgent re-transplantation is indicated
- acute and chronic rejection, ischemia-reperfusion injury
- vascular – hepatic artery or portal vein thrombosis, IVC obstruction
- biliary complications – fever, increasing bilirubin and ALP
- recurrence of hepatitis B – prophylactic medical therapy is usually effective in preventing recurrence in graft; hepatitis C anti-recurrence therapy is less effective but recurrence can be controlled medically

Prognosis

- patient survival at 1 year – 85%
- graft survival at 1 year – 60-70%, at 5 years – 40-50%

Biliary Tract

Cholelithiasis

Definition

- the formation of gallstones (see Figure 25)

Pathogenesis

- imbalance of cholesterol and its solubilizing agents (bile salts and lecithin)
- excessive hepatic cholesterol secretion \rightarrow bile salts and lecithin are “overloaded” \rightarrow supersaturated cholesterol can precipitate and form gallstones
- North America: cholesterol stones (80%), pigment stones (20%)

Risk Factors

- cholesterol stones:
 - obesity, age <50
 - estrogens: female, multiparity, OCPs
 - ethnicity: First Nations heritage > Caucasian > Black
 - terminal ileal resection or disease (e.g. Crohn's disease)
 - impaired gallbladder emptying: starvation, TPN, DM type I
 - rapid weight loss: rapid cholesterol mobilization and biliary stasis
- pigment stones (contain calcium bilirubinate):
 - cirrhosis
 - chronic hemolysis
 - biliary stasis (strictures, dilation, biliary infection)



Summary of Biliary Tract Conditions

Gall Bladder	Asymptomatic Pain Only	Infection + Pain
Cholelithiasis	✓ (majority)	
Biliary Colic		✓
Cholecystitis		✓
Common Bile Duct	Asymptomatic Pain Only	Infection + Pain
Cholelithiasis	✓ (majority)	✓
Cholangitis		✓ (majority)



Risk factors for cholesterol stones
“4F’s”: Fat, Female, Fertile, Forties

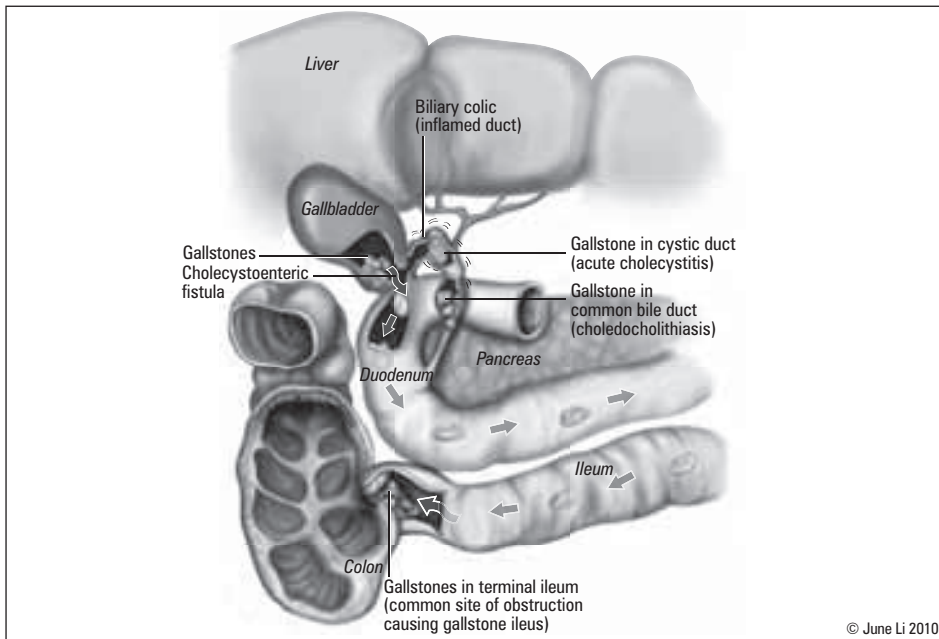


Figure 25. Gallstones

Clinical Features

- asymptomatic (80%):
 - most do NOT require treatment
 - consider cholecystectomy if: porcelain (calcified) gallbladder (25% risk of malignancy), sickle cell disease, pediatric patient, having bariatric surgery, diabetes, immunosuppression
- biliary colic (10-25%)
- cholecystitis
- choledocholithiasis (8-15%)
- cholangitis
- gallstone pancreatitis (see *Acute Pancreatitis*, GS49)
- gallstone ileus

Investigations

- U/S – diagnostic procedure of choice:
 - image for signs of inflammation, obstruction, localization of stones
- ERCP (endoscopic retrograde cholangiopancreatography):
 - visualization of upper GI tract, ampullary region, biliary and pancreatic ducts
 - method for treatment of CBD stones in periampullary region
 - complications: traumatic pancreatitis (1-2%), pancreatic or biliary sepsis
- MRCP (magnetic resonance cholangiopancreatography):
 - same information gained as ERCP but non-invasive
 - cannot be used for therapeutic purposes
- PTC (percutaneous transhepatic cholangiography):
 - injection of contrast via needle passed through hepatic parenchyma
 - useful for proximal bile duct lesions or when ERCP fails or not available
 - requires prophylactic antibiotics
 - contraindications: coagulopathy, ascites, peri/intrahepatic sepsis, disease of right lower lung or pleura
 - complications: bile peritonitis, chylothorax, pneumothorax, sepsis, hemobilia
- HIDA scan (hepatobiliary imino-diacetic acid scan):
 - used less commonly
 - radioisotope technetium-99 injected into a vein is excreted in high concentrations into bile, allowing visualization of the biliary tree
 - does not visualize stones; diagnosis by seeing occluded cystic duct or CBD



U/S is diagnostic procedure of choice for imaging the biliary tree.

Biliary Colic

Pathogenesis

- gallstone transiently impacted in cystic duct, no infection

Clinical Features

- steady pain in epigastrium or RUQ for minutes to hours, crescendo-decrescendo pattern
- frequently occurs at night or after fatty meal
- can radiate to right shoulder or scapula
- patients often restless
- no peritoneal findings, no systemic signs



Biliary colic is a constant pain not colicky.

Does this Patient have Acute Cholecystitis?

JAMA 2003; 289:80-86

Study: Looking at the ability of the clinical exam and basic laboratory findings to determine which patients need diagnostic imaging techniques to diagnose acute cholecystitis.

Selection criteria: Studies from 1966-2002 which evaluated the history, physical and basic laboratory tests in adult patients with abdominal pain or suspected acute cholecystitis. These studies had to have a control group with no diagnosis of acute cholecystitis. Acute cholecystitis was diagnosed through several different modalities (e.g. surgery, pathologic examination, etc.). This included 17 articles.

Results: No clinical or laboratory finding was sufficient to rule in or rule out the diagnosis of acute cholecystitis. The best finding for ruling in was positive Murphy's sign (LR+ = 2.8 95% CI 0.8-86) and the best test for ruling out was absence of right upper quadrant tenderness (LR - 0.4 95% CI 0.2-1.1), but neither of these findings were statistically significant. No study looked at the combination of clinical and laboratory findings.

Conclusion: No single clinical findings or laboratory test can rule in or rule out the diagnosis of acute cholecystitis. It is through a combination of clinical findings and diagnostic imaging that the diagnosis of acute cholecystitis is made in patients presenting with abdominal pain.

Laparoscopic vs. Open Cholecystectomy**Laparoscopic Cholecystectomy**

Shorter operating time
Shorter length of stay
Shorter sick leave
Shorter time to return to daily activities
Less postoperative pain*
Decreased use of postoperative analgesia*
Decreased reduction in pulmonary function*
Fewer pulmonary complications
Decreased acute phase response
Less impairment in intestinal motility*

Open Cholecystectomy

Lower conversion rates to open surgery (for mini-laparotomies)

***NOTE:**

Postoperative pain = measured on visual analog scale
Analgesic use = patient-controlled morphine consumption
Pulmonary function = O₂ consumption, spirometric parameters, arterial blood gases, and acid-base balance
Intestinal motility = auscultating intestinal peristalsis, abdominal circumference measurement, and time interval to restitution of defecation



Acute cholecystitis is treated with antibiotics and early cholecystectomy

Biliary colic is treated with analgesia and elective cholecystectomy

Investigations

- normal blood work: CBC, electrolytes, LFTs, bilirubin, amylase
- U/S shows cholelithiasis, may show stone in cystic duct

Treatment

- analgesia, rehydration during colic episode
- elective cholecystectomy (95% success):
 - complications: CBD injury (0.3-0.5%), hollow viscus injury, bile peritonitis, vessel injury
 - laparoscopic cholecystectomy is the standard of care
 - risk of open cholecystectomy higher in emergency situations

Acute Cholecystitis**Pathogenesis**

- inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or Hartmann's pouch
- no cholelithiasis in 5-10% (see *Acalculous Cholecystitis*, GS47)

Clinical Features

- often have history of biliary colic
- severe constant (hours to days) epigastric or RUQ pain, anorexia, nausea, vomiting, low grade fever (<38.5°C)
- focal peritoneal findings: Murphy's sign, palpable, tender gallbladder (in 33%)
- Boas' sign: right subscapular pain

Investigation

- bloodwork: elevated WBC and left shift, mildly elevated bilirubin, AST, ALT, ALP
- U/S:
 - 98% sensitive, consider HIDA scan if U/S negative
 - features on U/S (5 signs):
 - ♦ distended gallbladder
 - ♦ pericholecystic fluid
 - ♦ stone in cystic duct
 - ♦ thickened gallbladder wall (>3 mm)
 - ♦ sonographic Murphy's Sign – maximum tenderness on inspiration when probe over gallbladder

Complications

- gallbladder mucocele (hydrops) – long term cystic duct obstruction results in mucous accumulation in gallbladder (clear fluid)
- gangrene, perforation – result in abscess formation or peritonitis
- empyema of gallbladder – suppurative cholecystitis, pus in gallbladder + sick patient
- cholecystoenteric fistula, from repeated attacks of cholecystitis, can lead to gallstone ileus
- emphysematous cholecystitis – bacterial gas present in gallbladder lumen, wall or pericholecystic space (risk in diabetic patient)
- Mirizzi's syndrome – extra-luminal compression of CBD/CHD due to large stone in cystic duct

Treatment

- admit, hydrate, NPO, NG tube (if persistent vomiting from associated ileus), analgesics once diagnosis is made
- antibiotics:
 - *E. coli*, *Klebsiella*, *Enterococcus* and *Clostridium* account for >80% of infections
 - ampicillin + gentamicin OR Cipro® + Flagyl®
- cholecystectomy:
 - early (within 72 hrs) vs. delayed (after 6 weeks)
 - ♦ equal morbidity and mortality
 - ♦ early cholecystectomy preferred: shorter hospitalization and recovery time
 - ♦ emergent OR indicated if high risk, e.g. emphysematous, diabetic patient
 - laparoscopic is standard of care (convert to open for complications or difficult case)
 - ♦ laparoscopic: reduced risk of wound infections, shorter hospital stay, reduced post-op pain, increased risk of bile duct injury
- intra-operative cholangiography (IOC):
 - indications: clarify bile duct anatomy, obstructive jaundice, history of biliary pancreatitis, small stones in gallbladder with a wide cystic duct (>15 mm), single faceted stone in gallbladder, bilirubin >137 µmol/L
- percutaneous cholecystostomy tube: critically ill or if general anesthetic contraindicated

Acalculous Cholecystitis

Definition

- acute or chronic cholecystitis in the absence of stones

Pathogenesis

- typically due to gallbladder stasis → sludge forms in gallbladder

Risk Factors

- DM, immunosuppression, ICU admission, trauma patient, TPN, sepsis

Clinical Features

- see *Acute Cholecystitis*, GS46
- occurs in 20% of cases of acute cholecystitis

Investigations

- U/S: shows sludge in gallbladder, other U/S features of cholecystitis (see *Acute Cholecystitis*, GS46)
- CT or HIDA scan

Treatment

- cholecystectomy
- if patient unstable → cholecystostomy

Choledocholithiasis

Definition

- stones in common bile duct (CBD)

Clinical Features

- 50% asymptomatic
- often have history of biliary colic
- tenderness in RUQ or epigastrium
- acholic stool, dark urine, fluctuating jaundice
- primary vs. secondary stones:
 - primary: formed in bile duct, indicates bile duct pathology (e.g. benign biliary stricture, sclerosing cholangitis, choledochal cyst)
 - secondary: formed in gallbladder (85% of cases in U.S.)

Investigations

- CBC: usually normal; leukocytosis suggests cholangitis
- LFTs: increased bilirubin, ALP
- amylase/lipase: to rule out gallstone pancreatitis
- U/S: intra/extra-hepatic duct dilatation
- ERCP, PTC
- MRCP (90% sensitive, almost 100% specific, not therapeutic)

Complications

- cholangitis, pancreatitis, biliary stricture and biliary cirrhosis

Treatment

- if no evidence of cholangitis: treat with ERCP for CBD stone extraction possibly followed by elective cholecystectomy in 25% of patients

Acute Cholangitis

Pathogenesis

- obstruction of CBD leading to biliary stasis, bacterial overgrowth, suppuration and biliary sepsis

Etiology

- choledocholithiasis (60%), stricture, neoplasm (pancreatic or biliary), extrinsic compression (pancreatic pseudocyst or pancreatitis), instrumentation of bile ducts (PTC, ERCP), biliary stent
- organisms: *E. coli*, *Klebsiella*, *Pseudomonas*, *Enterococcus*, *B. fragilis*, *Proteus*

Clinical Features

- Charcot's triad – fever, RUQ pain, jaundice
- Reynolds' pentad – fever, RUQ pain, jaundice, shock, confusion
- may have nausea, vomiting, abdominal distention, ileus, acholic stools, tea-coloured urine

Investigations

- CBC: elevated WBC + left shift
- may have positive blood cultures
- LFTs: obstructive picture (elevated ALP and conjugated bilirubin, mild increase in AST, ALT)
- amylase/lipase: rule out pancreatitis
- U/S: intra/extra-hepatic duct dilatation



Charcot's Triad
Fever, RUQ pain, jaundice.



Reynolds' Pentad
Fever, RUQ pain, jaundice, shock, confusion.

**Common Bacteria in Biliary Tract****KEEPS**

Klebsiella
Enterococcus
E. Coli, *Enterobacter*
Proteus, *Pseudomonas*
Serratia

Treatment

- initial: NPO, fluid and electrolyte resuscitation, \pm NG tube, IV antibiotics
- decompression:
 - ERCP + sphincterotomy – diagnostic and therapeutic
 - PTC with catheter drainage – if ERCP not available or unsuccessful
 - laparotomy with CBD exploration and T-tube placement if above fails
- all patients should also have a cholecystectomy, unless contraindicated

Prognosis

- suppurative cholangitis – mortality rate: 50%

Gallstone Ileus

Pathogenesis

- repeated inflammation causing a cholecystoenteric fistula (usually duodenal) \rightarrow large gallstone enters the gut and impacts at or near the ileocecal valve, causing a true bowel obstruction (note: ileus is a misnomer in this context)

Clinical Features

- crampy abdominal pain, nausea, vomiting (see *Bowel Obstruction*, GS23)

Investigations

- AXR: dilated small intestine, air fluid levels, may reveal radiopaque gallstone, air in biliary tree (40%)
- CT: biliary tract air, obstruction, gallstone in intestine

Treatment

- fluid resuscitation, NG decompression
- surgery: enterotomy and removal of stone, inspect small and large bowel for additional proximal stones
- fistula usually closes spontaneously
- elective cholecystectomy after recovery if patient experiences gallbladder symptoms

Carcinoma of the Gallbladder

Risk Factors

- chronic symptomatic gallstones (70% of cases), old age, female, gallbladder polyps, porcelain gallbladder

Clinical Features

- majority are adenocarcinoma
- may be incidental finding on elective cholecystectomy (~1% of elective cholecystectomies)
- many patients are asymptomatic until late
- local: vague RUQ pain, \pm palpable RUQ mass
- systemic: jaundice (50%) due to invasion of CBD or compression of CBD by pericholedochal nodes, weight loss, malaise, anorexia
- early local extension to liver, may extend to stomach, duodenum
- early metastasis common to liver, lung, bone

Investigations

- U/S: mural thickening, calcification, loss of interface between gallbladder and liver, fixed mass
- endoscopic U/S (EUS): good for distinguishing carcinomas from other diagnoses such as polyps, good for staging, allows sampling of bile for cytology
- abdominal CT: polypoid mass, mural thickening, liver invasion, nodal involvement, distant mets

Treatment

- if carcinoma of the gallbladder is suspected preoperatively, an open cholecystectomy should be done to avoid tumour seeding of trocar sites
- confined to mucosa (rare) – cholecystectomy
- beyond mucosa – cholecystectomy, en bloc wedge resection of 3-5 cm underlying liver, dissection of hepatoduodenal lymph nodes

Prognosis

- poor 5-year survival (10%) as gallbladder carcinoma is often detected late

**Bouveret's Syndrome**

Gastric outlet/duodenal obstruction caused by a large gallstone passing through a cholecystogastric or cholecystoduodenal fistula.

Cholangiocarcinoma

Definition

- malignancy of extra intrahepatic bile ducts

Risk Factors

- age 50-70, gallstones, ulcerative colitis, primary sclerosing cholangitis, choledochal cyst, *Clonorchis sinensis* infection (liver fluke)

Clinical Features

- majority are adenocarcinoma
- gradual signs of biliary obstruction: jaundice, pruritis, dark urine, pale stool
- anorexia, weight loss, RUQ pain, Courvoisier's sign (if CBD obstructed), hepatomegaly
- early metastases are uncommon, but commonly tumour grows into portal vein or hepatic artery
- Klatskin tumour – cholangiocarcinoma located at bifurcation of common hepatic duct

Investigations

- LFTs show obstructive picture
- U/S, CT: bile ducts usually dilated, but not necessarily
- ERCP or PTC: to determine resectability, for biopsies
- CXR, bone scan: for metastatic workup

Treatment

- generally palliative
- if resectable: biliary drainage and wide excision margin
 - upper third lesions: duct resection + Roux-en-Y hepaticojejunostomy, ± liver resection
 - middle third lesions (uncommon): duct resection + Roux-en-Y hepaticojejunostomy
 - lower third lesions: Whipple procedure
- unresectable lesions: stent or choledochojejunostomy (surgical bypass)

Prognosis

- radiotherapy useful for additional palliation, chemotherapy may be helpful
- the more proximal to the liver, the worse the prognosis
- overall 5-year survival – 15%



Obstructive jaundice is the most common presenting symptom for cholangiocarcinoma.



Courvoisier's Sign

Palpable, nontender distended gallbladder due to CBD obstruction. Present in 33% of patients with pancreatic carcinoma. The distended gallbladder could not be due to acute cholecystitis or stone disease because the gallbladder would actually be scarred and smaller, not larger.

Pancreas



Acute Pancreatitis

- see Gastroenterology, G48

GALLSTONE PANCREATITIS

Pathogenesis

- obstruction of pancreatic duct by large or small gallstones and biliary sludge
- backup of pancreatic enzymes can cause autodigestion of the pancreas

Clinical Features (pancreatitis of any etiology)

- pain (epigastric pain radiating to back), nausea, vomiting, ileus, peritoneal signs, jaundice, fever
- Ingelfinger's sign: pain worse when supine, better when sitting forward
- rarely may have coexistent cholangitis or pancreatic necrosis
- Ranson's criteria for determining prognosis of acute pancreatitis (see sidebar)

Investigations

- high amylase (higher than alcoholic pancreatitis), lipase, high liver enzymes, leukocytosis
- U/S may show multiple stones (may have passed spontaneously), edematous pancreas
- CXR, AXR, CT (if severe to evaluate for complications)

Treatment

- supportive
- NPO, hydration, analgesia and antibiotics for severe cases of necrotizing pancreatitis or signs of sepsis
- stone often passes spontaneously (~90%); usually no surgical management in uncomplicated acute pancreatitis
- cholecystectomy during same admission after acute attack has subsided (25-60% recurrence if no surgery)



Ranson's Criteria

A. At admission

1. Age >55 years
2. WBC >16 x 10⁹/L
3. Glucose >11 mmol/L
4. LDH ≥350 IU/L
5. AST >250 IU/L

B. During initial 48 hours

1. Hct drop >10%
2. BUN rise >1.8 mmol/L
3. Arterial PO₂ <60 mmHg
4. Base deficit >4 mmol/L
5. Calcium <2 mmol/L
6. Fluid sequestration >6 L

C. Interpretation

- ≥2 – difficult course
- ≥3 – high mortality

- may need urgent ERCP + sphincterotomy if failure of conservative management (no benefit has been shown for early ERCP + sphincterotomy if no obstructive jaundice is present)
- surgical indications in acute pancreatitis (rare):
 - debridement and drain placement for necrotizing pancreatitis if refractory to medical management, if septic or in ICU without other sources of sepsis

Complications

- pseudocyst (collection of pancreatic secretions >4 weeks old surrounded by a defined wall of granulation tissue)
- abscess/infection, necrosis
- splenic/mesenteric/portal vessel thrombosis or rupture
- pancreatic ascites/pancreatic pleural fluid effusion
- diabetes
- ARDS/sepsis/multiorgan failure
- coagulopathy/DIC
- encephalopathy
- severe hypocalcemia

Chronic Pancreatitis

- see also Gastroenterology, G50

Surgical Treatment

- treatment is generally medical
- indications for surgery:
 - failure of medical treatment
 - debilitating abdominal pain
 - pseudocyst complications: persistence, hemorrhage, infection, rupture
 - CBD obstruction (e.g. strictures), duodenal obstruction
 - pancreatic fistula, variceal hemorrhage secondary to splenic vein obstruction
 - rule out pancreatic cancer
 - anatomical abnormality causing recurrent pancreatitis
- pre-op CT and/or ERCP are mandatory to delineate anatomy
- surgical options:
 - drainage procedures – only effective if ductal system is dilated
 - ♦ endoscopic duct decompression
 - ♦ Puestow procedure (longitudinal pancreatojejunostomy) – improves pain in 80% of patients
 - pancreatectomy – best option in absence of dilated duct
 - ♦ proximal disease – Whipple procedure (pancreatoduodenectomy): pain relief in 80%
 - ♦ distal disease – distal pancreatectomy ± Roux-en-Y pancreatojejunostomy
 - ♦ total pancreatectomy – refractory disease
 - nerve ablation:
 - ♦ celiac plexus block – lasting benefit in 30% patients, much less invasive
- pseudocyst (most resolve spontaneously with pancreatic rest):
 - cyst wall must be mature (4-6 weeks)
 - internal drainage (preferred): Roux-en-Y cyst-jejunostomy or cyst-gastrostomy
 - external drainage: may require second operation to treat pancreatic fistula
 - consider biopsy of cyst wall to rule out cystadenocarcinoma



The hallmark of chronic pancreatitis is epigastric pain radiating to the back.

Pancreatic Cancer

Epidemiology

- fourth most common cause of cancer-related mortality in both men and women in Canada in 2007 (Canadian Cancer Society)
- male:female = 1.7:1, average age: 50-70

Risk Factors

- increased age
- smoking – 2-5x increased risk, most clearly established risk factor
- high fat/low fibre diets, heavy alcohol use
- DM, chronic pancreatitis
- chemicals: betanaphthylamine, benzidine
- African descent

Clinical Features

- head of the pancreas (70%):
 - weight loss, obstructive jaundice, vague constant mid-epigastric pain (often worse at night, may radiate to back)
 - painless jaundice (occurs more often with peri-ampullary), Courvoisier's sign (see sidebar GS49)
 - palpable tumour mass → generally incurable
- body or tail of pancreas (30%):
 - tends to present later and usually inoperable
 - weight loss, vague mid-epigastric pain
 - <10% jaundiced
 - sudden onset diabetes



Vague abdominal pain with weight loss ± jaundice in a patient over 50 years old is pancreatic cancer until proven otherwise.

Investigations

- serum chemistry non-specific: elevated ALP and bilirubin >300 µmol/L
- U/S, contrast CT (also evaluates metastasis and resectability), ERCP

Pathology

- ductal adenocarcinoma – most common type (75-80%); exocrine pancreas
- intraductal papillary mucinous neoplasm (IPMN)
- other: mucinous cystic neoplasm (MCN), acinar cell carcinoma, islet-cell (insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma)

Treatment

- resectable (20% of pancreatic cancer)
 - no involvement of liver, peritoneum or vasculature (hepatic artery, SMA, SMV, portal vein, IVC, aorta), no distant metastasis
 - Whipple procedure (pancreatoduodenectomy) for cure – 5% mortality (Figure 26)
 - distal pancreatectomy ± splenectomy, lymphadenectomy if carcinoma of midbody and tail of pancreas
- non-resectable (palliative → relieve pain, obstruction)
 - most body/tail tumours are not resectable (due to late presentation)
 - relieve biliary/duodenal obstruction with endoscopic stenting or double bypass procedure (choledochoenterostomy + gastroenterostomy)
 - chemotherapy (gemcitabine), radiotherapy – only slightly increase survival



Whipple Procedure (Pancreatoduodenectomy)

1. Removal

Choledochoectomy
Cholecystectomy
Duodenectomy
Distal pancreatectomy
± Distal gastrectomy

2. New Connections

Hepaticojejunostomy (connect common hepatic duct to jejunum post cholecystectomy)
Pancreaticojejunostomy (connect distal pancreas remnant)
Gastrojejunostomy

Prognosis

- most important prognostic indicators are lymph node status, size >3 cm, perineural invasion (invasion of tumour into microscopic nerves of pancreas)
- overall 5 year survival is 1%
- average survival – 6 months if unresected, 12-18 months with curative resection

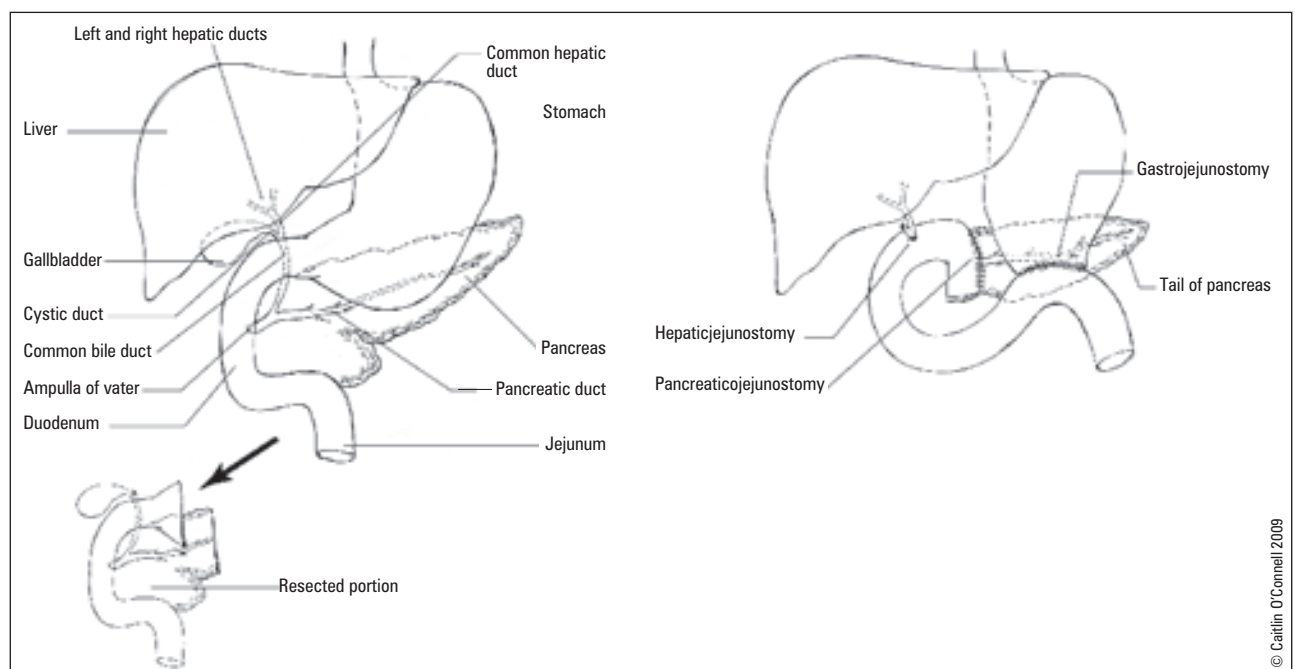


Figure 26. Schematic of Whipple Resection, Showing the Resected Components

Spleen

Splenic Trauma

- typically from blunt trauma (especially in people with splenomegaly)
- most common intra-abdominal organ injury in blunt trauma
- may have Kehr's sign: left shoulder pain due to diaphragmatic irritation from splenic rupture

Treatment

- in stable patients – extended bed rest with serial hematocrit levels, close monitoring
- hemostatic control
- splenic artery embolization
- splenorrhaphy (suture of spleen) – if patient hemodynamically stable, patient has stopped bleeding and laceration does not involve hilum
- partial splenectomy
- total splenectomy if patient unstable or high-grade injury

Splenectomy

Indications

- splenic trauma (most common reason for splenectomy), hereditary spherocytosis, primary hypersplenism, chronic immune thrombocytopenia purpura (ITP), splenic vein thrombosis causing esophageal varices, splenic abscess, thrombotic thrombocytopenia purpura (TTP), non-Hodgkin's lymphoma, primary splenic tumour (rare)
- does not benefit all thrombocytopenic states (e.g. infection, most malignancies involving the bone marrow, drugs/toxins)
- probability of cure of ITP by splenectomy is 60-70%, may be predicted by response to IVIg

Complications

- short-term:
 - atelectasis of left lower lung, bleeding, infection
 - injury to surrounding structures (e.g. gastric wall, tail of pancreas)
 - post-op thrombocytosis, leukocytosis
 - subphrenic abscess
- long-term:
 - post-splenectomy sepsis (encapsulated organisms): 4% of splenectomized patients
 - 50% mortality
 - pre-op prophylaxis with vaccinations (pneumococcal, *H. influenzae* and meningococcus)
 - liberal use of penicillin especially in children <6 years old

Breast



Levels of Axillary Lymph Nodes
Level I: lateral to pectoralis minor
Level II: deep to pectoralis minor
Level III: medial to pectoralis minor
 (Higher level = worse prognosis)

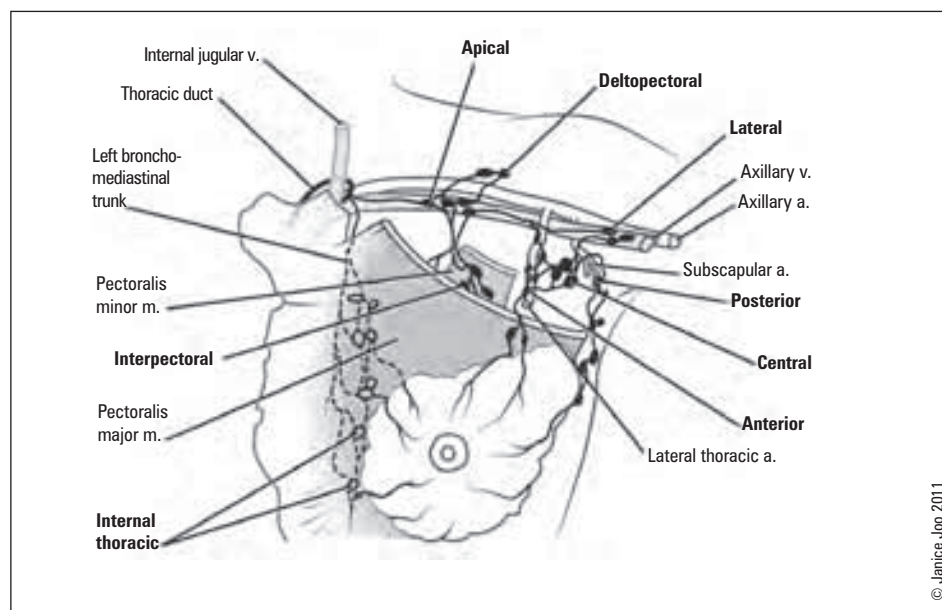


Figure 27. Anatomy of the Breast

Benign Breast Lesions

NON-PROLIFERATIVE LESIONS

- aka fibrocystic change, chronic cystic mastitis, mammary dysplasia
- benign breast condition characterized by fibrous and cystic changes in the breast
- no increased risk of breast cancer
- age 30 to menopause (and after if HRT used)
- clinical features:
 - breast pain, focal areas of nodularity or cysts often in the upper outer quadrant, frequently bilateral, mobile, varies with menstrual cycle, nipple discharge (straw-like, brown or green)
- treatment:
 - evaluation of breast mass and reassurance
 - if >40 years old: mammography every 3 years
 - no strong evidence for avoidance of xanthine-containing products (coffee, tea, chocolate, cola)
 - analgesia (ibuprofen, ASA)
 - for severe symptoms: OCP, danazol, bromocriptine



DDx for Breast Mass

- Breast Ca
- Fibrocystic changes
- Fibroadenoma
- Fat necrosis
- Papilloma/papillomatosis
- Galactocele
- Duct ectasia
- Ductal/lobular hyperplasia
- Sclerosing adenosis
- Lipoma
- Neurofibroma
- Granulomatous mastitis (e.g. TB, Wegener's, sarcoidosis)
- Abscess
- Silicone implant

PROLIFERATIVE LESIONS – No Atypia

Fibroadenoma

- most common benign breast tumour in women under age 30
- risk of subsequent breast cancer is increased only if fibroadenoma is complex, there is adjacent atypia or a strong family history of breast cancer
- clinical features:
 - nodules: smooth, rubbery, discrete, well-circumscribed, non-tender, mobile, hormone dependent
 - unlike cysts, needle aspiration yields no fluid
- investigations:
 - core or excisional biopsy required
 - ultrasound and FNA alone cannot differentiate fibroadenoma from phyllodes tumour
- treatment:
 - generally conservative: serial observation
 - consider excision if size 2-3 cm and rapidly growing on serial ultrasound, if symptomatic or patient preference

Intraductal Papilloma

- solitary intraductal benign polyp
- present as nipple discharge (most common cause of spontaneous, unilateral bloody nipple discharge), breast mass, nodule on U/S
- can harbour areas of atypia or DCIS
- treatment: excision of involved duct to ensure no atypia

Ductal Hyperplasia Without Atypia

- increased number of cells within the ductal space
- cells retain benign cytology
- no treatment required
- slightly increased cancer risk if moderate or florid hyperplasia

PROLIFERATIVE LESIONS – With Atypia

Atypical Hyperplasias

- can involve ducts (ductal hyperplasia with atypia) or lobules (lobular hyperplasia with atypia)
- cells lose apical-basal orientation
- increased risk of breast cancer
- diagnosis: core or excisional biopsy
- treatment: complete resection, risk modification (avoid exogenous hormones), close follow-up

OTHER LESIONS

Fat Necrosis

- uncommon, result of trauma (may be minor, positive history in only 50%), after breast surgery (i.e. reduction)
- firm, ill-defined mass with skin or nipple retraction, ± tenderness
- regress spontaneously, but complete imaging ± biopsy to rule out carcinoma

Mammary Duct Ectasia

- obstruction of a subareolar duct leading to duct dilation, inflammation, and fibrosis
- may present with nipple discharge, bluish mass under nipple, local pain
- risk of secondary infection (abscess, mastitis)
- resolves spontaneously

Montgomery Tubercle

- Montgomery tubercles aka Morgagni tubercles are papular projections at the edge of the areola
- obstruction of these glands can lead to inflammation or cystic collections (cyst of Montgomery aka retroareolar cyst)
- if signs of secondary infection, start treatment for mastitis
- resolves spontaneously in weeks to years

Abscess

- lactational (see Obstetrics, OB50) vs. periductal/subareolar
- unilateral localized pain, tenderness, erythema, subareolar mass, nipple discharge, nipple inversion
- rule out inflammatory carcinoma, as indicated
- treatment: initially broad-spectrum antibiotics and I&D, if persistent total duct excision (definitive)
- if mass does not resolve: fine needle aspiration (FNA) to exclude cancer, U/S to assess for presence of abscess

Breast Cancer

Gender followed by age are the two greatest risk factors for breast cancer.

Epidemiology

- 2nd leading cause of cancer mortality in women (1st is lung cancer)
- 1/9 women in Canada will be diagnosed with breast cancer in their lifetime
- 1/27 women in Canada will die from breast cancer

Risk Factors

- gender (99% female)
- age (80% >40 years old)
- most important risk factors are prior history of breast cancer and/or prior breast biopsy (regardless of pathology)
- 1st degree relative with breast cancer (greater risk if relative was premenopausal)
- increased risk with high breast density, nulliparity, first pregnancy >30 years old, menarche <12 years old, menopause >55 years old
- decreased risk with lactation, early menopause, early childbirth
- radiation exposure (e.g. Mantle radiation for Hodgkin's disease)
- >5 years HRT

Investigations

- mammography
 - indications:
 - ♦ screening (see Table 15):
 - every 1-2 years for women age 50-69
 - positive family history in 1st degree relative: every 1-2 years starting 10 years before the youngest age of presentation
 - ♦ diagnostic: investigation of patient complaints (discharge, pain, lump)
 - ♦ follow-up after breast cancer surgery
 - findings indicative of malignancy:
 - ♦ mass that is poorly defined, spiculated border
 - ♦ microcalcifications
 - ♦ architectural distortion
 - ♦ interval mammographic changes
 - ♦ normal mammogram does not rule out suspicion of cancer based on clinical findings
- other radiographic studies:
 - ultrasound – differentiate between cystic and solid
 - MRI – high sensitivity, low specificity
 - galactogram/ductogram (for nipple discharge) – identifies lesions in ducts
 - metastatic workup as indicated (usually after surgery or if clinical suspicion of metastatic disease) – bone scan, abdo U/S, CXR, head CT



Any palpable dominant breast mass requires further investigation.



Diagnostic mammography is indicated in all patients, even in women <50 years old.

Table 15. Screening for Breast Cancer in Women of Average Risk

Test/Maneuver	Effectiveness	Level of Evidence	Recommendation
Mammography, with or without clinical examination*, women aged 40-49 years	Controversial, routine mammography with or without clinical examination, has not consistently been shown to reduce breast cancer mortality or overall mortality (7 RCTs, 7 meta-analyses)	RCTs (I)	Current evidence does not support the recommendation that screening mammography be included or excluded from the periodic health examination of women aged 40-49 with average risk of breast cancer (Grade C)
Mammography, with or without clinical examination*, women aged 50-69	Statistically significant reduction in breast cancer mortality (RR 0.76) though overall mortality not affected (7 RCTs, 5 meta-analyses)	RCTs (I)	Based on breast cancer-specific mortality, the Canadian Task Force on Preventative Health Care concluded there was good evidence for screening women aged 50-69 by mammography (and clinical breast exam).(Grade A) The best available evidence does not provide conclusive direction regarding annual versus biennial screening
Teaching of Breast Self-Examination (BSE) to women aged 40-69	Evidence of no benefit in terms of survival from breast cancer Evidence of increased number of physician visits and increased rate of benign biopsy results	RCTs (I) Non-RCTs (II-1) Cohort Studies (II-3) Case-control studies (II-3) RCTs (I) Non-RCTs (II-1)	Fair evidence of no benefit and good evidence of harm, therefore fair evidence not to recommend routine teaching of BSE from the periodic health examination (Grade D)

* The utility of adding clinical breast examination (CBE) to mammography is unclear. Some of the 7 RCTs carried out CBE and mammography in combination and some separately. As relative contributions of mammography and clinical breast exam are unknown, both maneuvers are recommended by the Canadian Task Force on Preventative Health Care.

Diagnostic Procedures

- needle aspiration: for palpable cystic lesions; send fluid for cytology if blood or cyst does not completely resolve
- U/S or mammography guided core needle biopsy (most common)
- fine needle aspiration (FNA): for palpable solid masses; need experienced practitioner for adequate sampling
- excisional biopsy: only performed as second choice to core needle biopsy; should not be done for diagnosis if possible

Genetic Screening

- consider testing for BRCA1/2 if:
 - patient diagnosed with breast AND ovarian cancer
 - strong family history of breast/ovarian cancer (e.g. Ashkenazi Jewish)
 - family history of male breast cancer
 - young patient (<35 years old)

Staging (see Table 16)

- clinical:
 - tumour size by palpation, mammogram
 - nodal involvement by palpation
 - metastasis by physical exam, CXR and abdo U/S (or CT chest/abdo/pelvis), bone scan (usually done post-op if node-positive disease)
- pathological:
 - tumour size
 - grade: modified Bloom and Richardson score (I to III) – histologic, nuclear and mitotic grade
 - number of axillary nodes positive for malignancy out of total nodes resected, extranodal extension, sentinel node positive/negative
 - estrogen receptor (ER) + progesterone receptor (PR) testing
 - Her2Neu receptor testing
 - margins: negative, <1 mm, positive
 - lymphovascular invasion (LVI)
 - extensive in situ component (EIC): DCIS in surrounding tissue
 - involvement of dermal lymphatics (inflammatory) – automatically Stage IIIB

A Comparison of Aspiration Cytology and Core Needle Biopsy According to Tumour Size of Suspicious Breast Lesions

Diagn Cytopathol 2008; 36(1):26-31

Background: The purpose of the study was to compare the accuracy of FNAC, CNB, and combined biopsy according to tumour size of suspicious breast lesions.

Methods: Ultrasound guided FNAC and CNB were performed in 264 patients with suspicious breast lesions from August, 1997 to August, 2002. The lesions were divided in four groups according to the tumour size in the histopathology report: lesions smaller than 1 cm, between 1 and 2 cm, between 2 and 5 cm, and lesions greater than 5 cm. The final surgical histopathology results identified 222 (84%) malignant cases and benign lesions summed 42 (16%).

Results: For lesions smaller than 1 cm, FNAC, CNB and combined biopsy were equivalent for all parameters. For lesions between 1 and 2 cm, FNAC and CNB were equivalent. Combined biopsy showed higher absolute sensitivity ($P = 0.007$) and lower inadequate rate ($P = 0.03$) when compared to FNAC. However, when combined biopsy and CNB were compared, no difference were found. For lesions between 2 and 5 cm, CNB showed higher absolute sensitivity ($P < 0.001$) and lower inadequate rate ($P < 0.007$) when compared to FNAC. Combined biopsy showed higher sensitivity compared to FNAC and CNB alone ($P < 0.05$) in this group. For lesions greater than 5 cm, FNAC and CNB were equivalent for all parameters. Combined biopsy only showed higher absolute sensitivity ($P = 0.04$) when compared with FNAC alone.

Conclusions: The combination of FNAC and CNB can improve the diagnosis of suspicious breast lesions greater than 1 cm. However, for lesions smaller than 1 cm, any modality has technical limitations.

Table 16. Staging of Breast Cancer (American Joint Committee on Cancer)

Stage	Tumour	Nodes (regional) (clinical)	Metastasis	Survival (5-year)
0	in situ	None	None	99%
I	<2 cm	None	None	94%
II A	<2 cm	Mobile ipsilateral	None	85%
II B	2-5 cm or >5 cm	None or mobile ipsilateral None	None None	70%
III A	Any size	Fixed ipsilateral or internal mammary	None	52%
III B	Skin/chest wall invasion	Any	None	48%
III C	Any size	Ipsilateral infraclavicular/internal mammary plus axillary nodes; ipsilateral supraclavicular node(s) ± axillary nodes	None	33%
IV	Any	Any	Distant	18%



Favourable Features	Unfavourable Features
<ul style="list-style-type: none"> • <2 cm • Grade I (low grade) • Node negative • Stage I • ER positive • Mucinous pattern 	<ul style="list-style-type: none"> • >5 cm • Grade III (high grade) • Node positive • Stage IV • ER negative • Inflammatory cancer • Her2Neu positive • Positive margins • LVI • EIC • Dermal lymphatics involved

Pathology

- non-invasive (cannot penetrate basement membrane):
 - ductal carcinoma *in situ* (DCIS):
 - ♦ proliferation of malignant ductal epithelial cells completely contained within breast ducts, often multifocal
 - ♦ 80% non-palpable, detected by screening mammogram
 - ♦ risk of invasive ductal carcinoma in same breast up to 35% in 10 years
 - ♦ treatment:
 - lumpectomy with wide excision margins + radiation (5-10% risk invasive cancer)
 - mastectomy if large area of disease, high grade or multifocal (risk of invasive cancer reduced to 1%)
 - possibly tamoxifen as an adjuvant treatment
 - 99% 5-year survival
 - lobular carcinoma *in situ* (LCIS):
 - ♦ neoplastic cells completely contained within breast lobule
 - ♦ no palpable mass, no mammographic findings, usually incidental finding on breast biopsy for another indication
 - ♦ treatment
 - clinical follow-up
 - chemoprevention (tamoxifen)
 - surgery (uncommon)
 - ♦ not a precursor lesion, but considered a risk factor for breast cancer development
- invasive:
 - invasive ductal carcinoma (most common 80%):
 - ♦ originates from ductal epithelium and infiltrates supporting stroma
 - ♦ characteristics: hard, scirrhous, infiltrating tentacles, gritty on cross-section
 - invasive lobular carcinoma (8-15%):
 - ♦ originates from lobular epithelium
 - ♦ 20% bilateral (i.e. more often than infiltrating ductal carcinoma)
 - ♦ does not form microcalcifications, harder to detect mammographically (may benefit from MRI)
 - Paget's disease (1-3%):
 - ♦ ductal carcinoma that invades nipple with scaling, eczematoid lesion
 - inflammatory carcinoma (1-4%):
 - ♦ ductal carcinoma that invades dermal lymphatics
 - ♦ most aggressive form of breast cancer
 - ♦ clinical features: erythema, skin edema, warm, swollen and tender breast ± lump
 - ♦ peau d'orange indicates advanced disease (IIb-IV)
 - male breast cancer (<1%):
 - ♦ most commonly invasive ductal carcinoma
 - ♦ often diagnosed at later stages
 - ♦ stage-for-stage similar prognosis to breast cancer in females
 - ♦ consider genetic testing
 - sarcomas: rare
 - ♦ most commonly phyllodes tumour, a variant of fibroadenoma with potential for malignancy
 - lymphoma: rare
 - other: papillary, medullary, mucinous, tubular cancers
 - ♦ generally better prognosis

Treatment

Table 17. Breast Cancer Treatment by Stage

Stage	Primary Treatment Options	Adjuvant Systemic Therapy
0 (<i>in situ</i>)	BCS + radiotherapy BCS alone if margins >1 cm and low nuclear grade Mastectomy* ± SLNB	None
I	BCS + axillary node dissection + radiotherapy Mastectomy* + axillary node dissection/SLNB	May not be needed; discuss risks/benefits of chemotherapy and tamoxifen
II	BCS + axillary node dissection + radiotherapy Mastectomy* + axillary node dissection/SLNB	Chemotherapy for premenopausal women or postmenopausal and estrogen receptor (ER) negative, follow by tamoxifen if ER positive
III	Likely mastectomy + axillary node dissection + radiotherapy	Neoadjuvant therapy may be considered i.e. preoperative chemotherapy and/or hormone therapy. Adjuvant radiation and chemotherapy may also be appropriate (i.e. post-op)
Inflammatory	Likely mastectomy + axillary node dissection + radiotherapy	Neoadjuvant therapy
IV	Surgery as appropriate for local control	Primary treatment is systemic therapy i.e. chemotherapy and/or hormone therapy

BCS = breast-conserving surgery; SLNB = sentinel lymph node biopsy

*If no reason to select mastectomy, the choice between BCS + radiotherapy and mastectomy can be made according to patient's preference since choice of local treatment does not significantly affect survival if local control is achieved

Primary Surgical Treatment

- breast-conserving surgery (BCS) – lumpectomy with wide local excision
 - for treatment of stage I and II disease
 - must be combined with radiation for survival equivalent to mastectomy
 - contraindications:
 - ♦ high risk of local recurrence – extensive malignant-type calcifications on mammogram, multifocal primary tumours, or failure to obtain tumour-free margins after re-excision
 - ♦ contraindications to radiation therapy (pregnancy, previous radiation, collagen vascular disease)
 - ♦ large tumour size relative to breast
- mastectomy
 - radical mastectomy (rarely done anymore) – removes all breast tissue, skin, pectoralis muscle, axillary nodes
 - modified radical mastectomy (MRM) – removes all breast tissue, skin, and axillary nodes
 - simple mastectomy – removes all breast tissue and skin
 - see Plastic Surgery, PL31 for breast reconstruction
- axillary lymph node dissection (ALND)
 - performed if SLNB is positive or nodes are clinically concerning
 - risk of arm lymphedema (10-15%), decreased arm sensation, shoulder pain
- sentinel lymph node biopsy (SLNB)
 - technetium-99 ± blue dye injected at tumour site prior to surgery to identify sentinel node(s)
 - intraoperative frozen section
 - proceed with ALND if positive
 - 5% false negative rate

Adjuvant/Neoadjuvant

- radiation
 - indications:
 - ♦ decrease risk of local recurrence; almost always used after BCS, sometimes after mastectomy (is >4 nodes positive or tumour >5 cm)
 - ♦ inoperable locally advanced cancer
 - axillary nodal radiation may be added if nodal involvement
- hormonal
 - indications:
 - ♦ ER positive plus node-positive or high-risk node-negative
 - ♦ palliation for metastases
 - tamoxifen if premenopausal or aromatase inhibitors (e.g. anastrozole)
 - ovarian ablation (e.g. goserelin/GnRH agonist, oophorectomy), progestins (e.g. megestrol acetate), androgens (e.g. fluoxymesterone) are other options
- chemotherapy
 - indications:
 - ♦ ER negative plus node-positive or high-risk node-negative
 - ♦ ER positive and young age
 - ♦ stage I disease at high risk of recurrence (high grade, lymphovascular invasion)
 - ♦ palliation for metastatic disease

Post-Treatment Follow-up

- visits q3-6 months x 2 years and annually thereafter (frequency is controversial)
- annual mammography; no other imaging unless clinically indicated
- psychosocial support and counselling

Local/Regional Recurrence

- recurrence in treated breast or ipsilateral axilla
- 1% per year up to maximum of 15% risk of developing contralateral malignancy
- 5x increased risk of developing metastases

Metastasis

- bone > lungs > pleura > liver > brain
- treatment is palliative: hormone therapy, chemotherapy, radiation



Breast conserving surgery can be offered to most women with stage I/II disease.

Twenty-year Follow-up of a Randomized Study comparing Breast-conserving Surgery with Radical Mastectomy for Early Breast Cancer

Veronesi U, et al. *NEJM* 2002; 16:1227-32

Background: Women enrolled in a randomized trial to compare the efficacy of radical mastectomy (RM) with that of breast-conserving surgery (BCS) were followed over a 20-year period for long-term outcomes including disease recurrence and survival.

Methods: From 1973-1980, 701 women with breast cancers measuring <2 cm in diameter were randomly assigned to undergo RM (349 patients) or BCS followed by radiotherapy to the ipsilateral breast (352 patients).

Results: Rates of ipsilateral disease recurrence were lower in patients treated with RM compared to BCS (crude cumulative incidence 2.3% versus 8.8% after 20 years, $P < 0.001$). However, there was no significant difference in rates of contralateral breast malignancies, metastatic spread, or second primary malignancies between the two groups. All-cause mortality rates were 41.7% in the BCS group and 41.2% in the RM group ($P = 1.0$), with mortality rates due to breast cancer of 26.1% and 24.3% respectively ($P = 0.8$).

Conclusions: The long-term survival rate among patients treated with breast-conserving surgery and adjuvant radiotherapy is the same as that among patients treated with radical mastectomy.



There is no survival benefit of mastectomy over lumpectomy plus radiation for stage I and II disease.

Surgical Endocrinology

Thyroid and Parathyroid

- see [Endocrinology](#), E28 and [Otolaryngology](#), OT32, OT34

Adrenal Gland

- see [Endocrinology](#), E35
- functional anatomy:
 - cortex: glomerulosa (mineralocorticoids), fasciculata (glucocorticoids), reticularis (sex steroids)
 - medulla: catecholamines (epinephrine, norepinephrine)
- types: functional (e.g. Cushing's syndrome, Conn's syndrome) or non-functional

INCIDENTALOMA

- adrenal mass discovered by investigation of unrelated symptoms

Epidemiology

- benign adenoma (38%) > metastases to adrenal (22%) >> cyst, carcinoma, pheochromocytoma, neuroblastoma
- metastasis to adrenal gland from: lung > breast, colon, lymphoma, melanoma, kidney
- peak incidence of carcinoma: females ages 50-60, risk decreases with increasing age and male gender

Investigations

- MRI, CT: size >6 cm is best predictor of primary adrenal carcinoma (92% are >6 cm)
- functional studies:
 - pheochromocytoma: 24 hour urine epinephrine, norepinephrine, metanephrine, normetanephrine, VMA (vanillylmandelic acid)
 - Cushing's: 24 hour urine cortisol or 1 mg overnight dexamethasone suppression test
 - aldosteronoma: electrolytes, aldosterone: renin level, saline suppression test if appropriate
 - adrenal androgens: 17-OH progesterone, DHEAS
- FNA biopsy: if suspect metastasis to adrenal (must exclude pheochromocytoma first)
 - indicated if history of cancer or patient is smoker
- iodocholesterol scintigraphy: may distinguish benign vs. malignant disease

Treatment

- functional tumour: resect
- non-functioning tumour:
 - >6 cm: resect
 - 3-6 cm: MRI (T2 density, shape, margins), more likely to resect in females and if <60 years old
 - <3 cm: follow with repeat CT in 12-18 months

Skin Lesions

- see [Dermatology](#), D6; [Emergency](#), ER17; [Plastic Surgery](#) PL14

Common Medications

Antiemetics

- dimenhydrinate (Gravol®) 25-50 mg PO/IV/IM q4-6h prn
- prochlorperazine (Stemetil®) 5-10 mg PO/IV/IM bid-tid prn
- metochlopramide (Maxeran®) 10 mg IV/IM q2-3h prn, 10-15 mg PO qid (30 min before meals and qhs)
- ondansetron (Zofran®)
- granisetron (Kytril®) 1 mg PO bid (for nausea from chemotherapy/radiation)

Analgesics

- acetaminophen ± codeine (Tylenol® #3/plain) 1-2 tabs q4-6h PO/PR prn
- morphine 2.5-10 mg IM/SC q 4-6h prn + 1-2 mg IV q1h prn for breakthrough
- ketorolac (Toradol®)
- Percocet® (acetaminophen/oxycodone, 325/5 mg) 1-2 tabs PO q4-6h prn

DVT Prophylaxis

- heparin 5000 units SC bid, if cancer patient then heparin 5000 units SC tid
- dalteparin (Fragmin®) 5000 units SC daily
- enoxaparin (Lovenox®) 40 mg SC daily

Antidiarrheals

- loperamide (Imodium®) 4 mg PO initially, then 2 mg PO after each loose stool up to 16 mg/d
- diphenoxylate + atropine (Lomotil®) 2 tabs/10 ml PO qid

Laxatives

- sennosides (Senokot®) 1-2 tabs qhs
- docusate sodium (Colace®) 100 mg PO bid
- glycerine supp 1 tab PR prn
- lactulose 15-30 ml PO qid prn
- milk of magnesia (MOM) 30-60 ml PO qid prn
- bisacodyl (Dulcolax®) 10-15 mg PO prn

Sedatives

- zopiclone (Imovane®) 5-7.5 mg PO qhs prn
- lorazepam (Ativan®) 0.5-2 mg PO/SL qhs prn

Antibiotics

- cefazolin (Ancef®) 1 g IV/IM on call to OR or q8h – GP except *Enterococcus*, GN only *E. coli*, *Klebsiella* and *Proteus*
- cefalexin (Keflex®) 250-500 mg PO qid – *Listeria*, GP except *Enterococcus*, GN only *E. coli*, *Klebsiella* and *Proteus*
- ceftriaxone 1-2 g IM/IV q24h – broad coverage including *Pseudomonas*
- ampicillin 1-2 g IV q4-6h – *Listeria*, GP (*Enterococcus*) except *Streptococcus* and *E. coli*, oral anaerobes except *Bacteroides*
- gentamicin 3-5 mg/kg/day IM/IV divided q8h; monitor creatinine, gentamicin levels – GN including *Pseudomonas*
- ciprofloxacin 400 mg IV q12h, 500 mg PO bid – GN including *Pseudomonas*
- metronidazole (Flagyl®) 500 mg PO/IV bid, (500 mg PO tid for *C. difficile*) – anaerobes
- clindamycin 600-900 mg IV q8h, 150-400 mg PO qid – GP except *Enterococcus*, anaerobes

Over-the-Counter Medications

- Pepto-Bismol® (bismuth subsalicylate) 2 tabs or 30 ml PO q30min-1hr up to 8 doses/day
 - side effects: black stools, risk of Reye's syndrome in children
- Alka-Seltzer® (ASA + citrate + bicarbonate) 2 tabs in 4 oz water PO q4h prn, max 8 tabs
- Maalox® (aluminum hydroxide + magnesium hydroxide) 10-20 ml or 1-4 tabs PO prn
- Tums® (calcium carbonate) 1-3 g PO q2h prn
- Rolaids® (calcium carbonate and magnesium hydroxide) 2-4 tabs PO q1h prn, max 12 tabs/day

References

- Andreoli TE et al. Cecil Essentials of Medicine. Fifth Edition. W.B. Saunders Co, Philadelphia 2001
- Bateson MC. Gallbladder disease. *BMJ*. 318:1745-8. 1999.
- Bazarah BM, Peltekian KM, McAlister VC et al. Utility of MELD and Child-Turcotte-Pugh Scores and the Canadian Waitlisting Algorithm in predicting short-term survival after liver transplant. *Clin Invest Med* 27(4): 162. 2004
- Bland KI et al. The Practice of General Surgery. First Edition. W.B. Saunders Co, Toronto. 2002.
- Canadian Task Force on Preventive Health Care. Colorectal cancer screening. *CMAJ*. 165(2):206-208. 2001
- Preoperative antibiotic prophylaxis. CDC website: www.cdc.gov/ncidod/hip/SSI/SSI.pdf
- Chandler C et al. Prospective evaluation of early versus delayed laparoscopic cholecystectomy for treatment of acute cholecystitis. *Am J Surg*. 66(9): 896-900. 2000.
- Classen DC et al. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *NEJM*. 326(5):281-6. 1992.
- Darouiche RO et al. Chlorhexidine-Alcohol versus Povidone-Iodine for Surgical-Site Antisepsis. *NEJM* 2010; 362:18-26.
- De Groen PC et al. Biliary tract cancers. *NEJM*. 341(18):1368-1378. 1999.
- Doherty GM. Current Surgical Diagnosis and Treatment, 12th ed. McGraw-Hill, New York, 2006.
- Edell SL and Eisen MD. Current imaging modalities for the diagnosis of breast cancer. *Delaware Med J*. 71:377-82. 1999
- Ferzoco LB et al. Acute diverticulitis. *NEJM*. 338(21):1521-26. 1998.
- Goldhirsch A et al. Meeting Highlights: International Consensus Panel on the Treatment of Primary Breast Cancer. *J Clin Oncol*, 19(18):3817-27, 2001.
- Graham DJ and McHenry CR. The adrenal incidentaloma: guidelines for evaluation and recommendations for management. *Surg Onc Clin North Am*. 7(4):749. 1998.
- Harken AH and Moore EE. Abemathy's Surgical Secrets. Hanley and Belfus, Inc. Philadelphia, 2000
- Hartmann LC et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *NEJM*. 340(2): 77-84. 1999.
- Hong Z, Wu J, Smart G, Kaita K, Wen SW, Paton S, Dawood M. Survival analysis of liver transplant patients in Canada 1997-2002. *Transplant Proc*. 38(9):2951-6. 2006.
- Hortobagyi GN. Treatment of breast cancer. *NEJM*. 339(14):974-984. 1998
- Ivanovich JI et al. A practical approach to familial and hereditary colorectal cancer. *Am J Med*. 107(1):68-77. 1999.
- Janne PA et al. Chemoprevention of colorectal cancer. *NEJM*. 342(26):1960-1968. 2000.
- Johnson CD. Upper abdominal pain: Gallbladder. *BMJ*. 323:1170-3. 2001.
- Kanwal F, Dulai GS, Spiegel BMR et al. A comparison of liver transplantation outcomes in the pre- vs. post-MELD eras. *Aliment Pharmacol Ther*. 21: 169-177. 2005.
- Kasper, Dennis L. Harrison's Principles of Internal Medicine. 16th ed. 2005.
- Kehlet H et al. Review of postoperative ileus. *Am J Surg*. 182(Suppl):3S-10S. 2001.
- King JE et al. Care of patients and their families with familial adenomatous polyposis. *Mayo Clin Proc*. 75(1):57-67. 2000
- Kosters JP, Gotsche PC. Regular self-examination or physical examination for early detection of breast cancer. *Cochrane Library*. 2, 2002.
- Latif A. Gastric Cancer Update on Diagnosis, Staging and Therapy. *Postgraduate Medicine*. 1997;102(4):231-6.
- Lawrence PF. Essentials of General Surgery. Lippincott Williams & Wilkins, Philadelphia, 2000.
- Levine CD. Toxic megacolon: diagnosis and treatment challenges. *AACN Clinical Issues*. 10(4):492-99. 1999
- Li CI, Anderson BO, Daling JR, Moe RE. Trends in Incidence Rates of Invasive Lobular and Ductal Breast Carcinoma. *JAMA*. 289(11): 1421-24. 2003.
- Madan AK et al. How early is early laparoscopic treatment of acute cholecystitis? *Am J Surg*. 183:232-236. 2002
- Mandel JS, Bond JH, Church TR, et al. Reducing Mortality from Colorectal Cancer by Screening for Fecal Occult Blood. Minnesota Colon Cancer Control Study. *NEJM*, 328(19):1365-71. 1993.
- Mandel JS, Church TR, Bond JH, et al. The Effect of Fecal Occult Blood Screening on the Incidence of Colorectal Cancer. *NEJM*, 343:1603-7). 2000
- Martin RF, Rossi RL. The Acute Abdomen: An Overview and Algorithms. *Surg Clin North Am*. 1997;77(6):1227-43.
- McDonnell SK. Efficacy of contralateral prophylactic mastectomy in women with a personal and family history of breast cancer. *J Clin Oncol*. 19(19):38-43, 2001.
- Olivetto I, Levine M. Clinical practice guidelines for the care and treatment of breast cancer: The management of ductal carcinoma in situ (summary of the 2001 update). *CMAJ* 165(7):912-913, 2001.
- Olsen O, Gotsche PC. Screening for breast cancer with mammography (Cochrane review) In: the Cochrane Library, Issue 3, 2003. Oxford: Update Software.
- Paulsan, EK et al. Suspected appendicitis. *NEMJ*. 348(3): 236-42. 2003 Jan 16.
- Paulson EK, Kalady MF, Pappas TN. Suspected Appendicitis. *NEJM*. 2003. Jan 16; 348(3):236-42.
- Polk H, Christmas B. Prophylactic antibiotics in surgery and surgical wound infections. *Am Surgeon*, 66(2): 105-111. 2000
- Ransohoff DF and Sandler RS. Screening for colorectal cancer. *NEJM*. 346(1):40-44. 2002
- Ringash J. Preventive health care, 2001 update: screening mammography among women aged 40-49 years at average risk of breast cancer. *CMAJ*. 164(4):469-76, 2001.
- Ross NS and Aron DC. Hormonal evaluation of the patient with an incidentally discovered adrenal mass. *NEJM*. 323:1401. 1990.
- Roy MA. Inflammatory bowel disease. *Surg Clin North Am*. 77(6):1419-1431. 1997
- Rubin BP, Heinrich MC, Corless CL. Gastrointestinal Stromal Tumour. *Lancet*. 2007. May 19; 369(9574):1731-41.
- Rustgi AK. Hereditary gastrointestinal polyposis and nonpolyposis syndromes. *NEJM*. 331(25):1694-1702. 1994.
- Saini S. Imaging of the hepatobiliary tract. *NEJM*. 336(26):1889-1894. 1997.
- Sheth SG and LaMont JT. Toxic megacolon. *Lancet*. 351: 509-513. 1998.
- Styblo TM, Wood WC. The management of ductal and lobular breast cancer. *Surgical Oncology*. 8(2): 67-75. 1999.
- The University of Cincinnati Residents. The Mont Reid Surgical Handbook. Mosby Inc., St. Louis, 1997.
- Veronesi U, et al. twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *NEJM*. 2002; 16:1227-32
- Waki, K. UNOS Liver Registry: ten year survivals. [HYPERLINK "javascript:AL_get\(this,%20'jour','%20'Clin%20Transpl.'"\);" Clin Transpl](#). 2006:29-39.
- Way, LW. Current Surgical Diagnosis and Treatment. 11th ed. 2003.

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Seniors in Canada and the U.S.

Health Status



Geriatric Giants
Memory
Falls
Incontinence
Polypharmacy



5 Is of Geriatrics
Immobility
Intellect
Incontinence
Iatrogenesis
Impaired homeostasis



Most Common Acute Disorders in the Elderly
Cardiovascular disease (CHF, CVA, MI)
Fracture (hip, vertebrae, wrist)
Medication-related
Pneumonia
Sepsis



Most Common Chronic Disorders in the Elderly
Arthritis
Cataracts and other visual problems
COPD
Cardiovascular disease
Diabetes Mellitus (Type 2)
Hearing impairment
Hypertension
Mental disorders
Orthopaedic disorders
Sinusitis

Table 1. Causes of Mortality and Morbidity in Canadian and American Seniors

Mortality (Can ¹ /US ²)	Morbidity ^{1,2}
1. Diseases of the heart and circulatory system (30.0/30.4%)	1. Hypertension
2. Malignant neoplasms (20.0/22.0%)	2. Arthritis
3. Cerebrovascular disease (8.0/7.4%)	3. Heart disease
4. Chronic lower respiratory disease (5.1/6.0%)	4. Diabetes
5. Accidents (2.9%) ¹	5. Ulcers
6. Alzheimer's (4.2/3.7%) ²	6. Stroke
	7. Asthma
	8. Allergies

¹Statistics Canada 2005 ²National Center for Health Statistics 2007

Physiology and Pathology of Aging

Table 2. Changes Occurring Frequently with Aging

System	Physiological Changes	Pathological Changes
Neurologic	Decreased wakefulness, decreased brain mass, cerebral blood flow	Increased insomnia, neurodegenerative disease, stroke, decreased reflex response
Special Senses	Decreased lacrimal gland secretion, lens transparency, dark adaptation, decreased sense of smell and taste	Increased glaucoma, cataracts, macular degeneration, presbycusis, presbyopia, tinnitus, vertigo, oral dryness
Cardiovascular	Increased sBP, dBP, decreased HR, CO Decreased vessel elasticity, cardiac myocyte size and number, beta-adrenergic responsiveness	Increased atherosclerosis, CAD, MI, CHF, hypertension, arrhythmias
Respiratory	Increased tracheal cartilage calcification, mucous gland hypertrophy Decreased elastic recoil, mucociliary clearance, pulmonary function reserve	Increased COPD, pneumonia, pulmonary embolism
Gastrointestinal	Increased intestinal villous atrophy Decreased esophageal peristalsis, gastric acid secretion, liver mass, hepatic blood flow, calcium and iron absorption	Increased cancer, diverticulitis, constipation, fecal incontinence, hemorrhoids, intestinal obstruction
Renal and urologic	Increased proteinuria, urinary frequency Decreased renal mass, creatinine clearance, urine acidification, hydroxylation of vitamin D, bladder capacity	Increased urinary incontinence, nocturia, BPH, prostate cancer, pyelonephritis, nephrolithiasis, UTI
Reproductive	Decreased androgen, estrogen, sperm count, vaginal secretion Decreased ovary, uterus, vagina, breast size	Increased breast and endometrial cancer, cystocele, rectocele, atrophic vaginitis
Endocrine	Increased NE, PTH, insulin, vasopressin Decreased thyroid and adrenal corticosteroid secretion	Increased DM, hypothyroidism, stress response
Musculoskeletal	Increased calcium loss from bone Decreased muscle mass, cartilage	Increased arthritis, bursitis, osteoporosis, polymyalgia rheumatica
Integumentary	Atrophy of sebaceous and sweat glands Decreased epidermal and dermal thickness, dermal vascularity, melanocytes, collagen synthesis	Increased lentigo, cherry hemangiomas, pruritus, seborrheic keratosis, herpes zoster, decubitus ulcers, skin cancer
Psychiatry	None	Increased depression, dementia, delirium, suicidality, substance abuse, anxiety, insomnia

Differential Diagnoses of Common Presentations



Constipation

- see Gastroenterology, G25

Definition

- less than 3 bowel movements in one week and/or hard stools, straining, sense of blockade, manual maneuvers or incomplete evacuation on more than 25% of occasions

Epidemiology

- chronic constipation increases with age (up to 1/3 of patients >65 years experience constipation)

Pathophysiology

- impaired rectal sensation
- colorectal dysmotility

Risk Factors

- immobility
- dehydration
- polypharmacy
- drugs – narcotics, calcium channel blockers
- low fibre/calorie diet
- obstructive lesions – bowel obstruction, cancer, diverticular disease, IBD, strictures
- altered colonic motility – IBS, colonic inertia
- neurological – sacral cord dysfunction, Parkinson's disease, stroke
- metabolic – diabetes, hypokalemia, hypercalcemia
- psychiatric – depression, dementia

Treatment

- non-pharmacological
 - increase fibre intake
 - adequate fluid intake
 - discourage chronic laxative use
 - regular exercise
 - review medication regime, reduce dosages or substitute
- pharmacologic
 - see *Common Medications*, GM14

Delirium, Dementia and Depression

- see Psychiatry, PS17, PS18, PS8 and Neurology, N10

Delirium Prevention in Elderly

- ensure optimal vision and hearing to support orientation (e.g. clean, appropriate eyewear and hearing aids)
- provide adequate nutrition and hydration
- encourage regular mobilization to build and maintain strength, balance and endurance
- avoid unnecessary medications and monitor for drug interactions
- avoid bladder catheterization if possible

Elder Abuse

Definition

- includes physical abuse, sexual abuse, emotional or psychological abuse, financial abuse, abandonment and neglect
- elder abuse is a criminal offence under the Criminal Code of Canada
- in the U.S., most states have criminal penalties for elder abuse, laws vary from state to state

Epidemiology

- in Canada, approximately 4% of elderly persons living in private homes have suffered abuse
- in the U.S., estimates of the frequency of elder abuse range from 3-8%
- physician reporting is mandatory only in Newfoundland, Nova Scotia and PEI; in Ontario, only abuse occurring in nursing homes is mandatory to report
- insufficient evidence to include/exclude screening in the Periodic Health Exam

**Red Flags for Elder Abuse**

1. Delay in seeking medical attention
2. Disparity in histories
3. Implausible or vague explanations
4. Frequent emergency room visits for exacerbations of chronic disease despite plan for medical care and adequate resources
5. Presentation of functionally impaired patient without designated caregiver
6. Lab findings inconsistent with history

Risk Factors

- situational factors
 - isolation, lack of money, lack of community resources for additional care, unsatisfactory arrangements
 - inadequate access to appropriate beds, low staff-to-patient ratio, low pay rates for staff, low educational level of staff, staff burnout
- characteristics of the victim
 - physical or emotional dependence on caregiver, lack of close family ties, history of family violence, age over 75 years, recent deterioration in health, dementia
- characteristics of the perpetrator
 - stress caused by financial, marital or occupational factors, deterioration in health, bereavement, substance abuse, mental illness, related to victim, living with victim, long duration of care for victim (mean 9.5 years)

Management

- assess safety and determine capacity to make decisions about living arrangements
- establish need for hospitalization or alternate accommodation (e.g. immediate risk of physical harm by self or caregiver)
- involve multidisciplinary team (e.g. nurse, social worker, family members and physicians including geriatrician, psychiatrist or family physician)
- contact local resources (e.g. legal aid, elderly advocacy centre, crisis centre)
- educate and assist caregiver, link up with community resources (e.g. personal support worker, homemaking services, caregiver support groups)

Failure to Thrive (Frailty)

**Four Syndromes in Failure to Thrive**

My Pa Can't Drive
 Malnutrition
 Physical impairment
 Cognitive impairment
 Depression

Definition

- declining independence and functional capacity with loss of vigor and/or weight in older adults
- not an inevitable consequence of aging

Etiology

- four syndromes are prevalent in older patients with failure to thrive: malnutrition, functional impairment, cognitive impairment and depression

**Functional Assessment (ADLs and IADLs)****ADLs: ABCDE-TT**

Ambulating
 Bathing
 Continence
 Dressing
 Eating
 Transferring
 Toileting

IADLs: SHAFT-TT

Shopping
 Housework
 Accounting/Managing finances
 Food preparation
 Transportation
 Telephone
 Taking medications

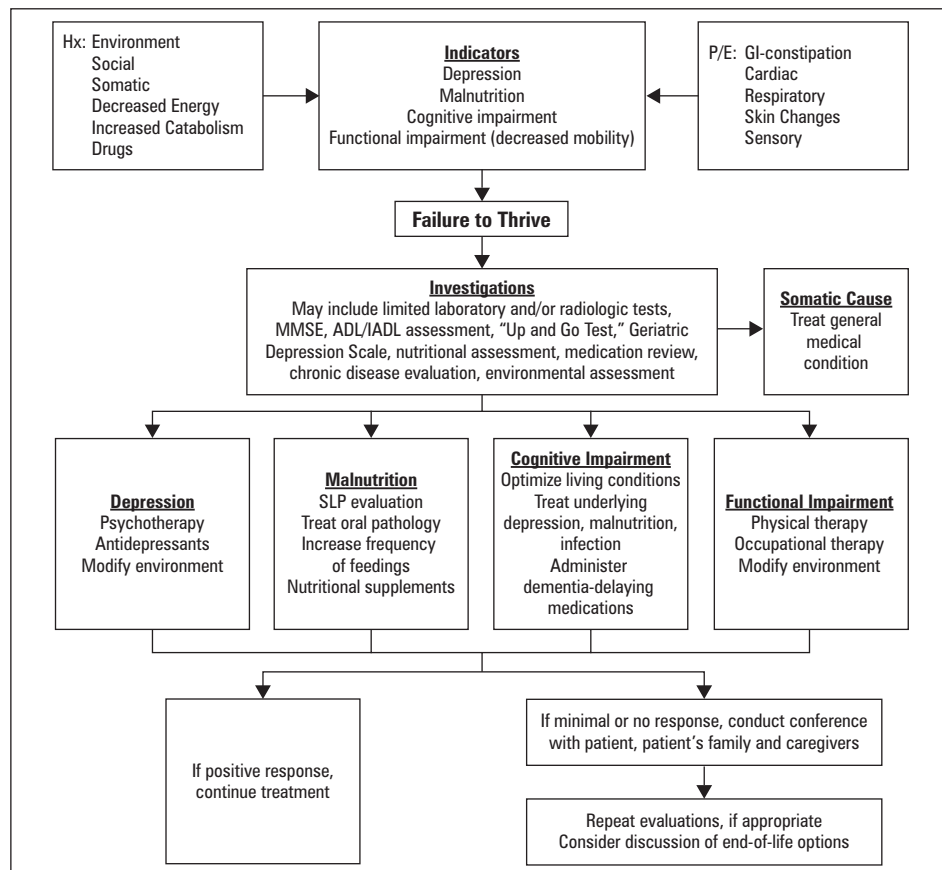


Figure 1. Evaluation of the Geriatric Patient who is Failing in the Community

Adapted from: Sarkisian CA, Lachs MS. "Failure to thrive" in older adults. *Ann Intern Med* 1996; 24:1072-1078.

Table 3. Common Medical Conditions Associated with Failure to Thrive

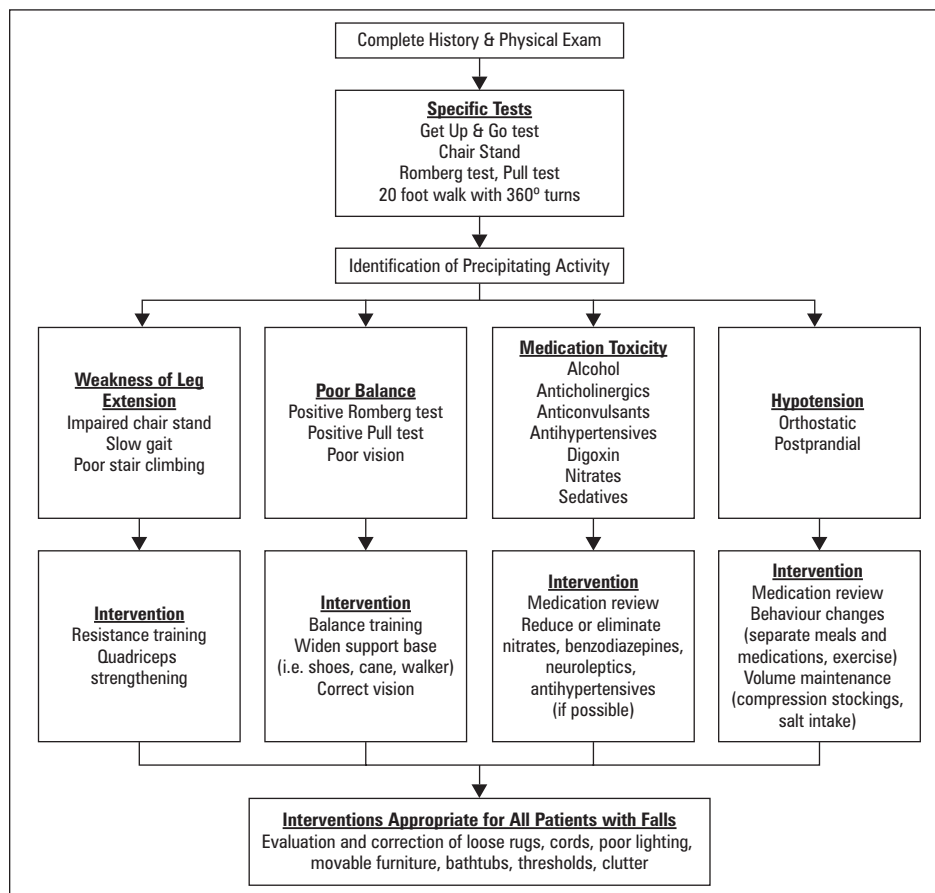
Medical Condition	Cause of Failure to Thrive
Cancer	Metastases, malnutrition, cachexia
Chronic lung disease	Respiratory failure
Chronic renal insufficiency	Renal failure
Chronic steroid use	Steroid myopathy, diabetes, osteoporosis, vision loss
Cirrhosis, hepatitis	Hepatic failure
Depression, other psychiatric disorder	Major depression, psychosis, poor functional status, cognitive loss
Diabetes	Malabsorption, poor glucose homeostasis, end-organ damage
Gastrointestinal surgery	Malabsorption, malnutrition
Hip, long bone fracture	Functional impairment
Inflammatory bowel disease	Malabsorption, malnutrition
Myocardial infarction, congestive heart failure	Cardiac failure
Recurrent UTI, pneumonia	Chronic infection, functional impairment
Rheumatologic disease (GCA, RA, SLE)	Chronic inflammation
Stroke	Dysphagia, depression, cognitive loss, functional impairment
Tuberculosis, other systemic infection	Chronic infection

Verdery RB. "Clinical evaluation of failure to thrive in older people." *Clin Geriatr Med* 1997; 13:769-78.

Falls

Epidemiology

- 30-40% of people >65 years old and ~50% of people >80 years old fall each year
 - approximately 20% of falls require medical attention
 - 5% of falls lead to hospitalization
 - 5-10% with serious injuries (e.g. hip fracture, head injury, laceration)
 - 1-2% of falls associated with hip fracture
 - 15% die in hospital, 33% 1-year mortality
 - between 25-75% do not recover to previous level of ADL function
 - mortality increases with age (171/100,000 in men >85 years old) and type of injury (25% with hip fracture die within 6 months)

**Figure 2. Approach to Falls in the Elderly**

Adapted from: Ganz, DA, Bao Y, Shekelle PE, Rubenstein LZ. Will my patient fall? *JAMA* 2007; 297: 77-86.

Tinetti ME, Baker DI, McAvay G, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community.

NEJM 1994; 331(13):821-827.



Key Physical Findings in the Elderly Patient Who Falls or Nearly Falls

I HATE FALLING

Inflammation of joints
Hypotension (orthostatic changes)
Auditory and visual abnormalities
Tremor
Equilibrium (balance) problem
Foot Problems
Arrhythmia, heart block or valvular disease
Leg-length discrepancy
Lack of conditioning (generalized weakness)
Illness
Nutrition
Gait disturbance

Fuller, G. Falls in the elderly.

Am Fam Phys 2001; 61(7): 2159-2172.



Drugs That May Increase the Risk of Falling

Sedative-hypnotic and anxiolytic drugs (especially long-acting benzodiazepines)
Tricyclic antidepressants
Major tranquilizers (phenothiazines and butyrophenones)
Antihypertensive drugs
Cardiac medications
Corticosteroids
Nonsteroidal anti-inflammatory drugs
Anticholinergic drugs
Hypoglycemic agents
Alcohol

Fuller, G. Falls in the elderly.

Am Fam Phys 2001; 61(7): 2159-2172.

Will My Patient Fall?

JAMA 2007; 297:77-86

Purpose: To identify the prognostic value of risk factors for future falls among older patients.

Study Selection: Prospective cohort studies of risk factors for falls that performed a multivariate analysis of such factors.

Results: Clinically identifiable risk factors were identified across 6 domains: orthostatic hypotension, visual impairment, impairment of gait or balance, medication use, limitations in basic or instrumental activities of daily living and cognitive impairment. Eighteen studies met inclusion criteria and provided a multivariate analysis including at least 1 of the risk factor domains. The estimated pretest probability of falling at least once in any given year for individuals 65 years and older was 27% (95% confidence interval, 19%-36%). Patients who have fallen in the past year are more likely to fall again [likelihood ratio range, 2.3-2.8]. The most consistent predictors of future falls are clinically detected abnormalities of gait or balance (likelihood ratio range, 1.7-2.4). Visual impairment, medication variables, decreased activities of daily living and impaired cognition did not consistently predict falls across studies. Orthostatic hypotension did not predict falls after controlling for other factors.

Conclusions: Screening for risk of falling during the clinical examination begins with determining if the patient has fallen in the past year. For patients who have not previously fallen, screening consists of an assessment of gait and balance. Patients who have fallen or who have a gait or balance problem are at higher risk of future falls.

**Fall Prevention Tips**

1. Improve lighting, especially on stairs
 2. Caution while adjusting to new bifocal prescription (poor depth perception)
 3. Siderails in bathtubs
 4. Railings on steps
 5. Connect patient to lifeline button signaling systems
 6. Remove loose mats or carpets, telephone cords and other tripping hazards
 7. Recommend support hose for varicose veins and swelling of ankles
- Goldlist B, Turpic I, Borins M. (1997). *Essential Geriatrics: Managing 6 conditions: Patient Care Canada*. 8(9).

Medication as a Risk Factor for Falls: Critical Systematic Review

J Gerontol A Biol Sci Med Sci 2007; 62(10):1172-81

Purpose: To review all original articles systematically examining medication use as a risk factor for falls or fall-related fractures in people aged more than 60 years.

Study Selection: Studies investigating "falls" or "accidental falls" and "pharmaceutical preparations" or specific groups of drugs were included. Studies not meeting the age criterion, not controlled with nonusers of target medicines or nonfallers, or with no clear definition of target medication were excluded.

Results: Twenty-eight observational studies and one randomized controlled trial met the inclusion criteria. The outcome measure was a fall in 22 studies and a fracture in 7 studies. The main group of drugs associated with an increased risk of falling was psychotropics: benzodiazepines, antidepressants, and antipsychotics. Antiepileptics and drugs that lower blood pressure were weakly associated with falls.

Conclusions: Central nervous system drugs, especially psychotropics, seem to be associated with an increased risk of falls. The quality of observational studies needs to be improved, as many appear to lack even a clear definition of a fall, target medicines, or prospective follow-up. Many drugs commonly used by older persons are not systematically studied as risk factors for falls.

Interventions for Preventing Falls in Older People Living in the Community

Cochrane Database Syst Rev 2009; 2:CD007146

Study: Cochrane systematic review. 11 RCT and quasi-RCT trials.

Population: 55,303 Patients over 60 or clearly elderly, senior, or older and living in the community.

Intervention: Any intervention to prevent falls.

Primary Outcomes: Rate of falls and number of fallers.

Results: Exercise is effective in reducing risk and rate of falls. Multifactorial assessment with a multi-professional team reduces rates of falls but not risk of falls. Limited evidence shows that environmental assessments and interventions may not reduce risk or rate of falls. Vitamin D does not appear to be effective in reducing rate of falls in all patients. Cardiac pacing in patients with carotid sinus hypersensitivity and history of syncope or falls reduces rate of falls. Home-based physiotherapy does not benefit patients with Parkinson's or stroke related mobility problems.

Conclusions: Exercise interventions reduce risk of falls in the elderly. Additional research is required to confirm and elaborate the contexts in which other interventions are effective.

Etiology

- commonly multifactorial
- extrinsic
 - environmental (e.g. home layout, lighting, stairs, footwear), accidental, abuse
 - medications/substances (e.g. alcohol)
 - month after hospital discharge, acute illness, exacerbation of chronic illness
- intrinsic
 - orthostasis/syncope
 - age-related changes and diseases associated with aging: musculoskeletal (arthritis, muscle weakness), sensory (visual, proprioceptive, vestibular), cognitive (depression, dementia, delirium, anxiety), cardiovascular (CAD, arrhythmia, MI, low BP), neurologic (stroke, decreased LOC, gait disturbances/ataxia), metabolic (glucose, electrolytes)

Investigations

- directed by history and physical
- CBC, electrolytes, BUN, creatinine, glucose, Ca, TSH, B12, urinalysis, cardiac enzymes, ECG, CT head

Prevention

- multidisciplinary, multifactorial, health and environment risk factor screening and intervention programs in the community
- program of muscle strengthening, balance retraining and group exercise programs (e.g. tai chi)
- home hazard assessment and modification (e.g. remove rugs, add shower bars, etc.)
- withdrawal of psychotropic medication
- cardiac pacing for those with cardio-inhibitory carotid sinus hypersensitivity
- optimize eyesight and footwear

Fecal Incontinence

Epidemiology

- second leading cause of nursing home placement

Etiology

- commonly multifactorial
- pelvic floor intact
 - neurologic conditions – age-related, neuropathy, multiple sclerosis, stroke, dementia
 - tumour/trauma (e.g. brain, spinal cord, cauda equina)
 - overflow (e.g. encopresis, impaction)
 - diarrheal conditions
- pelvic floor affected
 - trauma/surgery
 - nerve/sphincter damage
 - malformation, anorectal

Risk Factors

- prior vaginal delivery
- anorectal surgery
- pelvic radiation
- diabetes
- neurologic disease
- diarrheal conditions

Investigations (if cause not apparent from history and physical)

- stool studies
- endorectal ultrasound
- colonoscopy, sigmoidoscopy, anoscopy
- anorectal manometry/functional testing

Management

- diet/bulking agent if stool is liquid or loose
- disimpaction
- anti-diarrheal agents
- regular defecation program in patients with dementia
- counsel about biofeedback therapy (retraining of pelvic floor muscles)

Gait Disorders

- see Neurology, N36

Hazards of Hospitalization

Table 4. Recommendations for Sequelae of Hospitalization in Older Patients

Sequelae	Recommendations
Malnutrition	No dietary restrictions (except diabetes), assistance, dentures if necessary, eating out of bed
Urinary incontinence	Medication review, remove environmental barriers, discontinue use of catheter
Depression	Routine screening
Adverse drug event	Medication review
Confusion/delirium	Orientation, visual and hearing aids, volume repletion, noise reduction, early mobilization, medication review, remove restraints
Pressure ulcers	Low-resistance mattress, daily inspection, repositioning every 2 hours
Infection	Early mobilization, remove unnecessary IV lines, catheters, NG tubes
Falls	Appropriate footwear, assistive devices, early mobilization, remove restraints, medication review
Hypotension/dehydration	Early recognition and repletion
Diminished aerobic capacity/loss of muscle strength/contractures	Early mobilization
Decreased respiratory function	Incentive spirometry, physiotherapy

Hypertension

- see *Family Medicine*, FM35
- 60-80% of elderly (>65 years old) have hypertension
 - 60% of these have isolated systolic HTN
- non-pharmacologic treatments are first-line, then thiazide monotherapy is recommended
- add ACEI/ARB if also atherosclerosis, DM, CHF or chronic kidney disease
- add beta-blockers if also angina or CHF
- target BP: sBP <140, 65<dBP<90; for patients with DM: sBP <130, dBP <80

Immobility

Complications

- cardiovascular: orthostatic hypotension, venous thrombosis, embolism
- respiratory: decreased ventilation, atelectasis, pneumonia
- gastrointestinal: anorexia, constipation, incontinence, dehydration, malnutrition
- genitourinary: infection, urinary retention, bladder calculi, incontinence
- musculoskeletal: atrophy, contractures, bone loss
- skin: pressure sores
- psychological: sensory deprivation, delirium, depression

Immunizations

- the following immunizations are recommended for people 65 years of age and older
 - pneumococcus – 1 dose
 - influenza – every autumn
 - appropriate boosters (e.g. tetanus every 10 years)

Malnutrition

Definition

- involuntary weight loss of $\geq 5\%$ baseline body weight or ≥ 5 kg
- hypoalbuminemia, hypocholesterolemia

Etiology

- starvation
 - decreased intake: financial, psychiatric, cognitive deficits, functional deficits, anorexia associated with chronic disease
 - decreased assimilation: impaired transit, maldigestion, malabsorption
- stress
 - acute or chronic illness/infection, chronic inflammation, abdominal pain
- mechanical
 - dental problems, dysphagia

Treatment of Hypertension in Patients 80 Years of Age or Older

NEJM 2008; 358(18):1887-98

Study: Randomized, double-blind, placebo-controlled, multicentre trial.

Patients: 3845 patients who were 80 years of age or older and had a sustained systolic blood pressure of 160 mmHg were followed for a median 1.8 years.

Intervention: Indapamide (sustained release, 1.5 mg) or matching placebo. The angiotensin-converting enzyme inhibitor perindopril (2 or 4 mg), or matching placebo, was added if necessary to achieve the target blood pressure of 150/80 mmHg.

Primary Outcome: Fatal or nonfatal stroke.

Results: The mean age of the patients was 83.6 years and mean blood pressure while sitting was 173.0/90.8 mmHg. At 2 years, the mean blood pressure while sitting was 15.0/6.1 mmHg lower in the active treatment group than in the placebo group. Active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% confidence interval CI, -1 to 51; $p=0.06$), 39% reduction in the rate of death from stroke (95% CI, 1 to 62; $p=0.05$), 21% reduction in the rate of death from any cause (95% CI, 4 to 35; $p=0.02$), 23% reduction in the rate of death from cardiovascular causes (95% CI, -1 to 40; $p=0.06$), and 64% reduction in the rate of heart failure (95% CI, 42 to 78; $p<0.001$). Fewer serious adverse events were reported in the active-treatment group (358 vs. 448 in the placebo group; $p=0.001$).

Conclusions: Antihypertensive treatment with indapamide (sustained release), with or without perindopril, in persons 80 years of age or older reduces death from stroke, death from any cause and the incidence of heart failure.

Vaccines for Preventing Influenza in the Elderly

Cochrane Database Syst Rev 2006; 3:CD004876

Purpose: To review the evidence of efficacy, effectiveness and safety of influenza vaccines in individuals aged 65 years or older.

Study Selection: Randomized, quasi-randomized, cohort and case-control studies assessing efficacy against influenza (laboratory-confirmed cases) or effectiveness against influenza-like illness (ILI) or safety.

Results: Sixty-four studies were included in the efficacy/effectiveness assessment. Results were expressed as absolute vaccine efficacy (VE). In homes for elderly individuals (with good vaccine match and high viral circulation) the effectiveness of vaccines against ILI was 23% (6% to 36%) and non-significant against influenza (RR 1.04, 95% CI 0.43 to 2.51). In elderly individuals living in the community, vaccines were not significantly effective against influenza (RR 0.19, 95% CI 0.02 to 2.01), ILI (RR 1.05, 95% CI 0.58 to 1.89), or pneumonia (RR 0.88, 95% CI 0.64 to 1.20). Vaccine administration usually induced systemic side effects (general malaise, fever, nausea, headache) more frequently than placebo, but no outcome showed statistically significant results.

Conclusions: In long-term care facilities, where vaccination is most effective against preventing complications, the aims of the vaccination campaign are fulfilled, at least in part. The usefulness of vaccines in the community is modest.



Etiology of Malnutrition in the Elderly

MEALS ON WHEELS

Medications
Emotional problems
Anorexia
Late-life paranoia
Swallowing disorders
Oral problems
Nosocomial infections
Wandering/dementia related activity
Hyperthyroid/Hypercalcemia/
Hypoadrenalism
Enteric disorders
Eating problems
Low-salt/Low-fat diet
Stones



Calculating Basic Caloric and Fluid Requirements

WHO daily energy estimates for adults > 60 years:

Female: $10.5 \times (\text{weight in kg}) + 596$

Male: $13.5 \times (\text{weight in kg}) + 487$

Maintenance fluid requirements for the elderly without cardiac or renal disease: 1500-2500 cc/24hrs.

- age-related changes
 - appetite dysregulation, decreased thirst
- mixed
 - increased energy demands (e.g. hyperthyroidism), abnormal metabolism, protein-losing enteropathy

Risk Factors

- mechanical: dental problems, medical illnesses interfering with ingestion or decreasing appetite
- nutritional: medical illnesses increasing nutritional requirements or requiring dietary restrictions
- functional: difficulty shopping, preparing meals or feeding oneself due to functional impairment
- social: economic barriers to securing food, lack of availability of high quality food
- psychological: depression, poor appetite

Clinical Features

- history
 - recent weight loss, decreased food intake, constitutional symptoms, GI symptoms, recent or chronic illness, social factors
- physical examination
 - BMI <23.5 in males, <22 in females should raise concern
 - temporal wasting, muscle wasting, presence of triceps skin fold

Investigations

- CBC, electrolytes, Ca, Mg, PO₄, Cr, LFTs (albumin, INR, bilirubin), B₁₂, folate, TSH, transferrin, lipid profile, urinalysis

Osteoporosis

- see [Endocrinology](#), E43

Presbycusis

- see [Otolaryngology](#), OT20



Pressure Ulcers

- see also [Plastic Surgery](#), PL14

Risk Factors

- extrinsic factors: friction, pressure, shear force
- intrinsic factors: immobility, malnutrition, moisture, sensory loss

Table 5. Classification of Pressure Ulcers

Stage I	Changes include skin temperature, tissue consistency or sensation. An area of persistent erythema in lightly pigmented, intact skin. In darker skin, it may appear red, blue or purple.
Stage II	Partial thickness skin loss involving the epidermis, dermis or both. The ulcer is superficial and presents as an abrasion, blister or shallow crater.
Stage III	Full thickness skin loss involving damage or necrosis of subcutaneous tissue which may extend down to, but not through, underlying fascia. Presents as a deep crater with or without undermining of adjacent tissue.
Stage IV	Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures. May have associated undermining and/or sinus tracts.

Prevention

- pressure reduction
 - frequent repositioning
 - pressure-reducing devices (static, dynamic)
- maintaining nutrition, encouraging mobility and managing incontinence

Treatment

- minimize pressure on wound
- analgesia
- wound debridement (mechanical, enzymatic, autolytic) and dressing application
- maintain moist wound environment to enable re-epithelialization
- treatment of wound infections (topical gentamicin, silver sulfadiazine, mupirocin)

A Systematic Review of the Use of Hydrocolloids in the Treatment of Pressure Ulcers

J Clin Nurs 2008; 17(9):1164-73

Purpose: To describe the current evidence in the field of pressure ulcer treatment with hydrocolloids and to give recommendations for clinical practice and further research.

Study Selection: Randomized controlled trials on the treatment of pressure ulcers with hydrocolloids.

Results: Twenty-nine publications, dealing with 28 different studies, met the inclusion criteria and were included in the review. Hydrocolloids were most frequently used on pressure ulcers grades 2-3. Concerning the healing of the pressure ulcer, hydrocolloids are more effective than gauze dressings for the reduction of the wound dimensions. The absorption capacity, the time needed for dressing changes, the pain during dressing changes and the side-effects were significantly in favour of hydrocolloids compared to gauze dressings. Based on the available cost-effectiveness data, hydrocolloids are less expensive compared with collagen-, saline-, and povidone-soaked gauze but more expensive than hydrogel, polyurethane foam and collagenase.

Conclusions: Based on the studies included in this review, hydrocolloids are frequently used in the treatment of grades 2 and 3 pressure ulcers and are more effective and less expensive than gauze dressings. Compared with alginates, polyurethane dressings, less-contact layers, topical enzymes, and biosynthetic dressings, hydrocolloids are less effective.

- swab wounds not demonstrating clinical improvement for C&S; biopsy chronic wounds to rule out malignancy
- stage IV ulcers typically warrant surgical repair
- consider other treatment options
 - negative pressure wound therapy/vacuum-assisted closure (VAC)
 - biological agents: application of fibroblast growth factor, platelet-derived growth factor to wound
 - non-contact normothermic wound therapy
 - electrotherapy



Pressure-reducing Devices

Static devices distribute pressure over a greater surface area. Dynamic devices use alternating air currents to shift pressure to different body sites.

Urinary Incontinence

- see Urology, U5

Epidemiology

- 15-30% prevalence dwelling in community and at least 50% of institutionalized seniors
- morbidity: cellulitis, pressure ulcers, urinary tract infections, falls with fractures, sleep deprivation, social withdrawal, depression, sexual dysfunction
- not associated with increased mortality

Pathophysiology

- in general, occurs with age: decreased bladder capacity, increased post-void residual volume, increased involuntary bladder contractions (urge incontinence)
- in elderly women: decline in bladder outlet and urethral resistance pressure promoting stress incontinence
- in elderly men: prostatic enlargement can cause overflow and urge incontinence



Transient Causes of Incontinence

DIAPERS

Delirium
Infection
Atrophic urethritis/vaginitis
Pharmaceuticals
Excessive urine output
Restricted mobility
Stool impaction

Driving Competency



Reporting Requirements

- physician reporting to the Ministry of Transportation is mandatory in all provinces and territories except in Quebec, Nova Scotia and Alberta, where it is discretionary
- in Ontario, drivers >80 years old are not automatically required to pass a road test in order to renew their driver's license unless there are indications to suggest road safety risks; all drivers >80 years old must have a vision and knowledge test and participate in a 90-minute group education session to renew their license every 2 years
- in the U.S., varies by states, please refer to the AMA Physician's Guide to Assessing and Counseling Older Drivers for American recommendations, www.ama-assn.org/ama/pub/category/10791.html

Conditions That May Impair Driving

- alcohol
 - patients with a history of impaired driving and those deemed to have a high probability of future impaired driving should not drive any motor vehicle until further assessed
 - alcohol dependence or abuse: if suspected, should be advised not to drive
 - alcohol withdrawal seizure: must complete a rehabilitation program and remain abstinent and seizure-free for 6 months before driving
- blood pressure abnormalities
 - hypertension: sustained BP >170/110 should be evaluated carefully
 - hypotension: if syncopal, discontinue until attacks are treated and preventable
- cardiovascular disease
 - suspected asymptomatic CAD or stable angina: no restrictions
 - STEMI, NSTEMI with significant LV damage, coronary artery bypass surgery: no driving for one month following hospital discharge
 - NSTEMI with minor LV damage, unstable angina: no driving for 48 hours if percutaneous coronary intervention (PCI) performed or 7 days if no PCI performed
- cerebrovascular conditions
 - TIA: should not be allowed to drive until a medical assessment is completed
 - stroke: should not drive for at least one month; may resume driving if functionally able; no clinically significant motor, cognitive, perceptual or vision deficits; no obvious risk of sudden recurrence; underlying cause appropriately treated; no post-stroke seizure

Systematic Review of Driving Risk and the Efficacy of Compensatory Strategies in Persons with Dementia

J Am Geriatr Soc 2007; 55:878-84

Purpose: To determine whether persons with dementia are at greater driving risk and, if so, to estimate the magnitude of this risk and determine whether there are efficacious methods to compensate for or accommodate it.

Study Selection: Systematic review of the case-control studies of drivers with a diagnosis of dementia.

Results: Drivers with dementia universally exhibited poorer performance on road tests and simulator evaluations. The one study that used an objective measure of motor vehicle crashes found that the crash risk in persons with dementia was 2 to 2.5 times greater than matched controls. No studies were found that examined the efficacy of methods to compensate for or accommodate the decreased driving performance.

Conclusions: Drivers with dementia are poorer drivers than cognitively normal drivers, but studies have not consistently demonstrated higher crash rates. Clinicians and policy makers must take these findings into account when addressing issues pertinent to drivers with a diagnosis of dementia.



Key Factors to Consider in Older Drivers

SAFEDRIVE

Safety record

Attention (e.g. concentration lapses, episodes of disorientation)

Family observations

Ethanol abuse

Drugs

Reaction time

Intellectual impairment

Vision/Visuospatial function

Executive functions (e.g. planning, decision-making, self-monitoring behaviours)

Adapted from: Wiseman E.J. The older driver: a handy tool to assess competence behind the wheel. *Geriatrics*. 1996;51:36-45

- chronic obstructive pulmonary disease
 - mild/moderate impairment: no restrictions
 - moderate or severe impairment requiring supplemental oxygen: road test with supplemental oxygen
- cognitive impairment/dementia
 - moderate to severe dementia is a contraindication to driving; defined as the “inability to independently perform 2 or more IADLs or any basic ADL”
 - patients with mild dementia should be assessed; if indicated, refer to specialized driving testing centre; if deemed fit to drive, re-evaluate patient every 6-12 months
 - poor performance on MMSE, clock drawing or Trails B suggests a need to investigate driving ability further
 - MMSE score alone (whether normal or low) is insufficient to determine fitness to drive
- diabetes
 - diet controlled or oral hypoglycemic agents: no restrictions in absence of diabetes complications that may impair ability to drive (e.g. retinopathy, nephropathy, neuropathy, cardiovascular or cerebrovascular disease)
 - insulin use: may drive if no complications (as above) and no severe hypoglycemic episode in the last 6 months
- drugs
 - be aware of: analgesics, anticholinergics, anticonvulsants, antidepressants, antipsychotics, opiates, sedatives, stimulants
 - degree of impairment varies: patients should be warned of the medication/withdrawal effect on driving
- hearing loss
 - effect of impaired hearing on ability to drive safely is controversial
 - acute labyrinthitis, positional vertigo with horizontal head movement, recurrent vertigo: advise not to drive until condition resolves
- musculoskeletal disorders
 - physician's role is to report etiology, prognosis and extent of disability (pain, range of motion, coordination, muscle strength)
- post-operative
 - outpatient, conscious sedation: no driving for 24 hours
 - outpatient, general anesthesia: no driving for ≥24 hours
- seizures
 - first, single, unprovoked: no driving for 3 months until complete neurologic assessment, EEG, CT head
 - epilepsy: can drive if seizure-free on medication and physician has insight into patient compliance
- sleep disorders
 - if patient is believed to be at risk due to a symptomatic sleep disorder but refuses investigation with a sleep study or refuses appropriate treatment, the patient should not drive
- visual impairment
 - visual acuity: contraindicated to drive if <20/50 with both eyes examined simultaneously
 - visual field: contraindicated to drive if <120° along horizontal meridian and 15° continuous above and below fixation with both eyes examined simultaneously

N.B. guidelines included refer specifically to private driving; please see CMA guidelines for commercial driving

Health Care Institutions

- names of community health care institutions, types of facilities and services offered vary between geographical locations
- factors to consider when seeking services/institutions include level of care required, support networks, duration of stay and cost

Table 6. Classification of Health Care Services and Institutions

Institution/Service	Description
Community Support Services	Health care services offered at home for those who can live independently at home or under the care of family members including professional health care services, personal care and support (ADL assistance), homemaking (IADL assistance), community support services (e.g. transportation, meal delivery, day programs, caregiver relief, security checks, etc.)
Residential	Divided into short (<60-90 days/year) and long (indefinite) stay
a) Seniors Affordable Housing	Seniors who live independently and manage their own care but prefer to live near other seniors; usually has accessibility features and rent is adjusted based on income
b) Retirement/Nursing Home	Residents are fairly independent and require minimal support with ADLs and IADLs; often privately owned
c) Supportive Housing	Residents require minimal to moderate assistance with daily activities while living independently; often rental units in an apartment and may offer some physiotherapy and rehabilitation services
d) Long-term Care/Skilled Nursing Facility	Around the clock nursing care and on-call physician coverage; often offers occupational therapy, physiotherapy, respiratory therapy and rehabilitation services; may be used short-term for caregiver respite or for supportive patient care to regain strength and confidence after leaving the hospital
e) Hospice	Free-standing facility or designated floor in a hospital or nursing home for care of terminally ill patients and their families; focus is on quality of life and often requires prognosis ≤ 3 months

Palliative and End of Life Care



Principles and Quality of Life

- support, educate and treat both patient and family
- address physical, psychological, social and spiritual needs
- focus on symptom management and comfort measures
- offer therapeutic environment and bereavement support
- ensure maintenance of human dignity

End of Life Care Discussions

When to Initiate End of Life Care Discussions

- recent hospitalization for serious illness
- severe progressive medical condition(s)
- death expected within 6 to 12 months
- patient inquires about end of life care

Suggested Topics for Discussion

- goals of care (disease vs. symptom management)
- advance directives, power of attorney, public guardian and trustee
- treatment options and likelihood of success
- common medical interventions
 - mechanical ventilation
 - antibiotic therapy
 - feeding tubes
- resuscitation options and likelihood of success (Full Code vs. DNR status including preferences for CPR, intubation, ICU admission, artificial hydration)

Power of Attorney

- see Ethical, Legal and Organizational Aspects of Medicine, ELOAM4

Instructional Advance Directives

- see [Ethical, Legal and Organizational Aspects of Medicine](#), ELOAM4

Symptom Management

Table 7. Management of Common End-of-Life Symptoms

Symptom	Non-Pharmacologic Management	Pharmacologic Management
Constipation	Rule out obstruction, impaction, anorectal disease; hydration and high fibre intake; increase mobility	Stop unnecessary opioids and medications with anticholinergic side effects; provide stool softener (e.g. docusate sodium), increase peristalsis (e.g. senna), alter water and electrolyte secretion (e.g. magnesium hydroxide)
Death Rattle/Increased Pulmonary Secretions	Oral suctioning Discontinue unnecessary IV solutions	Scopolamine SC or transdermal
Dry mouth	Oral hygiene q2h, ice cubes, sugarless gum	Artificial saliva substitutes, bethanechol, pilocarpine 1% solution as mouth rinse
Dysphagia	Frequent small feeds, ideally seated, keep head of bed elevated for 30 minutes after eating, suction as necessary	Treat painful mucositis (diphenhydramine: lidocaine: Maalox® in a 1:2:8 mixture), candidiasis (fluconazole)
Dyspnea	Elevate head of bed, eliminate allergens, open window/use fan	Oxygen, bronchodilators, opioids (e.g. morphine, hydromorphone)
Hiccups	Dry sugar, breathing in paper bag	Chlorpromazine, haloperidol, metoclopramide, baclofen, marijuana
Nausea and Vomiting	Frequent and small meals, avoid offensive strong odours, treat constipation if present	Raised ICP: dexamethasone Anticipatory nausea, anxiety: lorazepam Vestibular disease, vertigo: dimenhydrinate Drug induced, hepatic or renal failure: prochlorperazine, haloperidol GERD: PPI or H2 antagonist Gastric stasis: metoclopramide Bowel obstruction: metoclopramide, dexamethasone, octreotide
Pain	Hot and cold compresses, music therapy, relaxation techniques, individualized program of physical activity designed to improve flexibility, strength and endurance	Nociceptive pain: non-opioids (NSAIDs, acetaminophen), weak opioids (codeine, hydrocodone, oxycodone), strong opioids (morphine, hydromorphone, oxycodone, fentanyl) Neuropathic pain: anticonvulsants (gabapentin, pregabalin), antidepressants (TCAs, SSRIs), steroids (dexamethasone) Bony pain: non-opioids, weak opioids, bisphosphonates, radiation therapy
Pruritus	Bathing with tepid water, avoid soap, bath oils; sodium bicarbonate for jaundice	Antihistamines, phenothiazines, topical corticosteroids, calamine lotion
Weakness	Modify environment and activities to decrease energy expenditure	Treat insomnia, anemia, depression; consider psychostimulants

AGS Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. *J Am Geriatr Soc* 2002; 50(6): Supplement.
Knowles, S. Symptoms management in palliative care. *On Continuing Practice* 1993; 20(1): 20-25.

Geriatric Pharmacology

Pharmacokinetics

Table 8. Age-Associated Pharmacokinetics

Parameter	Age Effect	Implications
Absorption (less significant)	Increased gastric pH Decreased splanchnic blood flow, GI absorptive surface and dermal vascularity; delayed gastric emptying	Drug-drug and drug-food interactions are more likely to affect absorption
Distribution	Increased total body fat and alpha1-glycoprotein Decreased lean body mass, total body water and albumin	Lipophilic drugs have a larger volume of distribution Decreased binding of acidic drugs, increased binding of basic drugs
Metabolism (less significant)	Decreased hepatic mass and hepatic blood flow; impaired phase I reactions (oxidative system)	Lower doses may be therapeutic
Elimination	Decreased renal blood flow, GFR, tubular secretion and renal mass	For every x% reduction in clearance, decrease the dose by x% and increase the interval by x%



Death Rattle

Noise caused by the oscillatory movement of mucous secretions in the upper airway with inspiration and expiration.



Nociceptive Pain

Somatic: localized to bone/skin/joint/muscle; gnawing, dull pain
Visceral: not well localized; crampy pain, pressure

Neuropathic Pain

Burning, shooting, radiating pain; localized to dermatomal regions



Opioid Equivalent Doses (to 10 mg of IV morphine)

Opioid	SC/IV dose	PO dose
Morphine	10 mg	20-30 mg
Codeine	Not recommended	180-240 mg
Oxycodone	Not recommended	10-15 mg
Hydromorphone	2 mg	4-6 mg

Fentanyl transdermal 25 microgram/hr = morphine 90 mg PO/24 hr, however fentanyl takes 12-16 hours to reach steady state
See *Clinical Pharmacology*, CP14 for complete chart.



Serum creatinine does not reflect creatinine clearance in the elderly.

Instead, use:

$CrCl = \frac{(\text{weight in kg})(140 - \text{age})(1.23)}{(\text{mL/min}) (\text{serum creatinine in } \mu\text{mol/L})}$

Multiply by 0.85 for females.



Benzodiazepines of Choice in the Elderly

LOT

Lorazepam

Oxazepam

Temazepam

Pharmacodynamics

Drug Sensitivity

- changes in pharmacokinetics as well as intrinsic sensitivity lead to altered drug responses
- increased sensitivity to warfarin, sedatives and narcotics
- decreased sensitivity to beta-blockers

Decreased Homeostasis

- poorer compensatory mechanisms leading to more adverse reactions (e.g. bleeding with NSAIDs/anticoagulants, altered mental status with anticholinergic/sympathomimetic/anti-Parkinsonian drugs)

Polypharmacy

Definition

- prescription, administration or use of many medications at the same time

Epidemiology

- in Canada, over 25% of elderly women and about 20% of elderly men reported using ≥ 3 medications
- hospitalized elderly are given an average of 10 medications during admission

Risk Factors for Non-Compliance

- risk of non-compliance correlates with medication factors, not age
 - number of medications – compliance with 1 medication is 80%, but drops to 25% with ≥ 6 medications
 - dosing, frequency
 - labelling, instructions, container design
 - financial constraints – medication cost and coverage (insurance, drug benefit plans)
 - cognitive impairment
 - sensory deprivation

Adverse Drug Reactions (ADRs)

- any noxious or unintended response to a drug that occurs at doses used for prophylaxis or therapy
- risk factors in the elderly
 - intrinsic: co-morbidities, age-related changes in pharmacokinetics and pharmacodynamics
 - extrinsic: number of medications, multiple prescribers, unreliable drug history
- 90% of ADRs are from: ASA, other analgesics, anticoagulants, antimicrobials, antineoplastics, digoxin, diuretics, hypoglycemics, steroids

Preventing Polypharmacy

- consider drug: safer side effect profiles, convenient dosing schedules, convenient route, efficacy
- consider patient: other medications, clinical indications, medical co-morbidities
- consider patient-drug interaction risk factors for ADRs
- review drug list regularly to eliminate medications with no clinical indication or with evidence of toxicity
- avoid treating an adverse drug reaction with another medication

Inappropriate Prescribing in the Elderly

Epidemiology

- the estimated prevalence of potentially inappropriate prescribing ranges from 12-40%

Beers Criteria

- examples include long-acting benzodiazepines, strong anticholinergics, high dose sedatives
- the elderly are also often under-treated (ACEI, ASA, beta-blockers, thrombolytics, warfarin)



Approach to Medication Review in the Elderly

NO TEARS

Need and indication

Open-ended questions (to get patient's perspective on medications)

Tests and monitoring (to assess disease control)

Evidence and guidelines

Adverse events

Risk reduction (of adverse events such as falls)

Simplification/switches



Principles for Prescribing in the Elderly

CARE

Caution/Compliance

Age (adjust dosage for age)

Review regimen regularly

Educate

Fordyce, M. *Geriatric Pearls*. Philadelphia: FA Davis Company, 1999.



Adverse drug reactions in the elderly may present as delirium, falls, fractures, urinary incontinence/retention or fecal incontinence/impaction.



Beers Criteria

48 medications to avoid in adults 65 and older due to safety concerns. For full list of medications, consult the following reference:

Fick DM, et al. Updating the Beers Criteria for potentially inappropriate medication use in older adults. *Arch Intern Med* 2003; 163: 2716-2724.

Common Medications

Table 9. Common Medications

Drug Name	Brand Name	Dosing Schedule	Indications	Contraindications	Side Effects	Mechanism of Action
Laxatives						
bran	All-Bran®	1 cup/day	Constipation		Bloating, flatus	Bulk-forming laxative
psyllium	Metamucil® Prodiem Plain®	1 tsp PO tid	Constipation, hypercholesterolemia	N/V, fever, abdo pain, obstruction	Bloating, flatus	Bulk-forming laxative
docusate	Colace® Docusoft®	100 mg PO bid	Constipation	Abdo pain, N/V, fever Not to be used with mineral oil	Mild cramps	Emollient, stool softener
lactulose	Chronulac® Cephulac® Kristalose®	15-30 cc PO daily/bid	Constipation, hepatic encephalopathy, bowel evacuation following barium exam	Patients on low galactose diets Abdo pain, N/V, fever	Flatus, cramps, nausea, diarrhea	Hyperosmolar agent, lowers pH of colon to decrease blood ammonia levels
senna	Senokot®/Ex-lax® Glyssennid®	1-2 tabs PO daily or 10-15 cc syrup PO daily	Constipation	Abdo pain, N/V, fever	Cramps, griping, dependence	Stimulant laxative
bisacodyl	Dulcolax®	5-15 mg PO (10 mg PR)	Constipation	Ileus, obstruction, abdo pain, N/V, fever, severe dehydration	Cramps, pain, diarrhea	Stimulant laxative
Analgesics (non-opioid)						
acetaminophen	Tylenol®	325-650 mg PO q4-6h prn (up to 4 g/day)	Fever, mild pain	Lower doses for hepatic and renal disease, chronic alcoholism, known hypersensitivity	Hepatotoxicity (in overdose)	Prostaglandin-synthesis inhibition, no anti-inflammatory effects
ibuprofen	Advil® Motrin®	200-800 mg PO q4-6h prn (up to 1200 mg/day)	Mild to moderate pain, inflammatory disorders, fever	Active GI bleed/ulcer disease, known hypersensitivity, severe renal or hepatic disease Geriatrics: more susceptible to adverse effects	Dyspepsia, nausea, diarrhea, dizziness, rash, GI toxicity (ulcer, perforation, bleed)	Prostaglandin-synthesis inhibition, anti-inflammatory effects
celecoxib	Celebrex®	OA: 200 mg PO daily or 100 mg PO bid	Osteoarthritis, rheumatoid arthritis, FAP	Cardiovascular or cerebrovascular disease, CABG (peri-op), sulfonamide or ASA/NSAID allergy, active GI bleed/ulcer severe renal or hepatic disease, hyperkalemia disease, IBD, severe renal or hepatic disease, hyperkalemia	GI symptoms (pain, diarrhea, dyspepsia, flatus), GI bleed, serious cardiovascular events	COX-2 inhibitor, analgesic, anti-inflammatory and anti-pyretic effects
Analgesics (opioid) – see Clinical Pharmacology, CP14						
Anti-hypertensives						
thiazide diuretic e.g. hydrochlorothiazide	Hydrazide®	12.5-25 mg PO daily	Hypertension, edema	Anuria, hepatic coma, pre-coma, known sensitivity to thiazides	Hypotension, transient hyperlipidemia, hypokalemia and other electrolyte disturbances, hyperuricemia, GI symptoms	Inhibition of Na/Cl co-transporter
ACEI e.g. ramipril	Altace®	2.5-10 mg PO daily	Essential hypertension, post-MI, cardiovascular disease, renal protection	Known hypersensitivity, angioedema	Hypotension, cough, headache, dizziness, asthenia, chest pain, nausea, peripheral edema, arthritis, dyspnea, angioedema, hyperkalemia	Inhibition of angiotensin-converting enzyme
ARB e.g. losartan	Cozaar®	50-100 mg PO daily	Essential hypertension (± diabetes mellitus)	Known hypersensitivity	Dizziness, hypotension, fatigue, headache, hyperkalemia	Antagonizes angiotensin II via blockade of the angiotensin type 1 receptor
DHP CCB e.g. amlodipine	Norvasc®	2.5-5 mg PO daily (initially)	Essential hypertension, chronic stable angina	Known hypersensitivity, severe hypotension, caution in aortic stenosis	Edema, muscle cramps, dizziness, headache, constipation, heartburn	Calcium ion influx inhibition

Table 9. Common Medications (continued)

Drug Name	Brand Name	Dosing Schedule	Indications	Contraindications	Side Effects	Mechanism of Action
Sleeping Medications						
zopiclone	Imovane® (Canada)	3.75 mg PO qhs (initially)	Insomnia	Known hypersensitivity, caution in myasthenia gravis, severe hepatic disease Geriatrics: dose reduction (dose-related adverse events)	Bitter taste, palpitations, vomiting, anorexia, sialorrhea, confusion, agitation, anxiety, tremor, sweating	Short-acting hypnotic (no tolerance effects)
temazepam	Restoril®	15 mg PO qhs	Short-term management of insomnia	Known hypersensitivity, myasthenia gravis, sleep apnea Geriatrics: dose reduction recommended	Drowsiness, dizziness, impaired coordination, hangover, lethargy, dependence	Benzodiazepine: generalized CNS depression mediated by GABA
lorazepam	Ativan®	0.5 mg PO qhs (initially, then increase)	Anxiety, insomnia	Known hypersensitivity, myasthenia gravis, narrow-angle glaucoma Geriatrics: dose reduction recommended	Dizziness, drowsiness, lethargy, dependence	Benzodiazepine: generalized CNS depression mediated by GABA
Cognitive Enhancers						
donepezil	Aricept®	5-10 mg PO daily	Mild to moderate dementia of Alzheimer's type	Known hypersensitivity, caution in pulmonary disease, sick sinus syndrome, seizure disorder	N/V, diarrhea, anorexia	Reversible inhibition of acetylcholinesterase
galantamine	Reminyl®	8-12 mg PO bid	Mild to moderate dementia of Alzheimer's type	Known hypersensitivity, caution in sick sinus syndrome, seizure disorder, pulmonary disease, low body weight	N/V, diarrhea, anorexia	Reversible inhibition of acetylcholinesterase
rivastigmine	Exelon®	1.5 mg PO daily (starting) up to 6 mg PO bid	Mild to moderate dementia of Alzheimer's type	Known hypersensitivity, severe hepatic disease, caution in sick sinus syndrome, pulmonary disease, seizure disorder	N/V, diarrhea, anorexia	Acetylcholinesterase inhibition (reversible but very slow)
memantine	Ebixa®/Namenda® (Cdn)/US	5 mg PO daily (starting) up to 10 mg PO bid	Moderate to severe dementia of Alzheimer's type	Known hypersensitivity, conditions that alkalize urine, caution in cardiovascular conditions	Agitation, fatigue, dizziness, headache, hypertension, constipation	NMDA-receptor antagonist

Parkinsonian Agents – see [Neurology, N27](#)

References

Health Status

Heron M. Deaths: Leading Causes for 2004. Health E-Stats. Released Nov 20, 2007.

Hoyert DL, Heron M, Murphy SL, Kung HC. (2006). Deaths: final data for 2003. Health E-stats. Released January 19, 2006.

Statistics Canada. (2005). Deaths, by selected grouped causes and sex, Canada, provinces and territories, annual. Ottawa: Canada.

Physiology and Pathology of Aging

Braunwald, E. Fauci, AS. Hauser, SL. Longo, DL. Jameson, JL. (Eds). (2004). Harrison's Principles of Internal Medicine. New York: McGraw-Hill.

Constipation

Higgins PDR, Johanson JF. (2004). Epidemiology of Constipation in North America: A Systematic Review. Am J Gastroenterol, 99:750-759.

Delirium, Dementia, and Depression

British Geriatrics Society and Royal College of Physicians. (2006). Guidelines for prevention, diagnosis and management of delirium in older people. Concise guidance to good practice series. No. 6.

Inouye, SK. (2007). The Hospital Elder Life Program. Retrieved May 4, 2010 from <http://elderlife.med.yale.edu/public/lifestyle.php?pageid=01.01.02>.

Elder Abuse

Health Canada. (2002). The Canadian Guide to Clinical Preventative Health Care. Ottawa: Canadian Task Force on Preventative Health Care.

Kergoat, MJ. (2000). Preventative Health Care in the Elderly. The Canadian Journal of CME.

Lachs MS, Pillemer K. (1995). Abuse and neglect of elderly persons. NEJM, 332(7):437-443.

Lachs M, Pillemer K. (2004). Elder Abuse. Lancet, 1192-1263.

Periodic health examination, 1994 update: 4. Secondary prevention of elder abuse and mistreatment. CMAJ, 151(10):1413-1420.

Sokol HN. (2008). Elder abuse. UpToDate. Schmorler KE (ed).

Sillman JS. Elder abuse. UpToDate.

Failure to Thrive

Robertson RG, Montagnini M. (2004). Geriatric failure to thrive. Am Fam Phys, 70(2): 343-348.

Sarkisian CA, Laches MS. (1996). "Failure to thrive" in older adults. Ann Intern Med, 124: 1072-1078.

Verdery RB. (1997). Clinical evaluation of failure to thrive in older people. Clin Geriatr Med, 13:769-78.

Falls

Close J, Ellis M, Hooper R, Glucksman E, Jackson S, Swift C. (1999). Prevention of falls in the elderly trial (PROFET): a randomized controlled trial. Lancet, 353(9147): 93-7.

Fuller, G. (2001). Falls in the elderly. Am Fam Phys, 61(7): 2159-2172.

Ganz, DA, Bao Y, Shekelle PE, Rubenstein LZ. (2007). Will my patient fall? JAMA, 297: 77-86.

Gillespie LD, Gillespie WJ, Robertson MC, Lamb SE, Cumming RG, Rowe BH. (2003). Interventions for preventing falls in elderly people. The Cochrane Database of Systematic Reviews, 4.

Goldlist B, Turpic I, Borins M. (1997). Essential Geriatrics: Managing 6 conditions: Patient Care Canada. 8(9): 61-74.

Hartikainen S, Lönnroos E, Louhivuori K. (2007). Medication as a risk factor for falls: critical systematic review. J Gerontol A Biol Sci, 62(10): 1172-81.

Kiel, DP. (2005). Overview of falls in the elderly. UpToDate. Rose, BD (Ed). UpToDate. Wellestly, MA.

Tinetti ME, Baker DI, McAvay G, et al. (1994). A multifactorial intervention to reduce the risk of falling among elderly people living in the community. NEJM, 331(13):821-827.

Hazards of Hospitalization

Creditor MC. (1993). Hazards of Hospitalization of the Elderly. *Ann Intern Med.* 118(3): 219-223.
Inouye AK, Bogardus ST, Charpentier PA, et al. (1999). A multi-component intervention to prevent delirium in hospitalized older patients. *NEJM*, 340(9):669-676.
Sager MA, Franke T, Inouye SK, et al. (1996). Functional outcomes of acute medical illness and hospitalization in older persons. *Arch Internal Med*, 156(6):645-52.

Hypertension

ALLHAT officers and coordinators for the ALLHAT collaborative research group. (2002). The antihypertensive and lipid-lowering treatment to prevent heart attack trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002 Dec 18;288(23):2981-97.
Appel, LJ, Espeland, MA, Easter, L, Wilson, AC, Folmar, S, Lacy, CR. (2001). Effects of reduced sodium intake on hypertension control in older individuals: results from the Trial of Nonpharmacologic Interventions in the Elderly (TONE). *Arch Intern Med*. 2001 Mar 12;161(5):685-93.
Beckett NS et al. (2008). Treatment of hypertension in patients 80 years of age or older. *NEJM*. 358(18):1887-98.
Folmar KC, S. Cutler, JA. (1998). Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). *JAMA*. 1998 Mar 18;279(11):839-46.
Heyneman A, Beele H, Vanderwee K, Defloor T. (2008). A systematic review of the use of hydrocolloids in the treatment of pressure ulcers. *J Clin Nurs*. 17(9):1164-73.
Kannel, WB. (1996). Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA*. 1996 May 22-29;275(20):1571-6.
Kaplan, NM, Rose, BD. (2005). Treatment of hypertension in the elderly. UpToDate. Rose, BD (Ed). UpToDate. Wellestly, MA.
Mulrow C, Lau J, Cornell J, Brand M. (2002). Pharmacotherapy for hypertension in the elderly (Cochrane Review). In: *The Cochrane Library*, Issue 2.
Whelton, PK, Appel, LJ, Espeland, MA, Applegate, WB, Ettinger, WH Jr, Kostis, JB, Kumanyika, S, Lacy, CR, Johnson, Canadian Hypertension Recommendations Working Group (2002). The 2001 Canadian hypertension recommendations. *Perspectives in Cardiology*. 38-46.

Immunizations

Rivetti D et al. (2006). Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev*. 19;3:CD004876

Malnutrition

Halsted, CH. (2004). Malnutrition and nutritional assessment. Pp. 411-415. *Harrison's Principles of Internal Medicine*. 16th edition. Kasper, DL.

Pressure Ulcers

Berlowitz, D. (2005). Pressure ulcers: staging; epidemiology; pathogenesis; clinical manifestations. UpToDate. Rose, BD (Ed). UpToDate. Wellestly, MA.

Driving Competency

AMA. (2006). Physicians Guide to Assessing and Counseling Older Drivers. National Highway Traffic Safety Administration.
CMA. (2006). Determining Medical Fitness to Drive: A Guide for Physicians. Ottawa.
Grabowski DC, Campbell CM, Morrissey MA (2004). Elderly Licensure Laws and Motor Vehicle Fatalities. *JAMA*. 291(3): 2840-2846.
Hogan DB. (2007). Systematic review of driving risk and the efficacy of compensatory strategies in persons with dementia. *J Am Geriatr Soc*. 55:878-84.

Health Care Institutions

Government of Ontario. (2007). Reports on Long-Term Care Homes. Queen's Printer for Ontario.

Palliative and End of Life Care

AGS Panel on Persistent Pain in Older Persons (2002). The management of persistent pain in older persons. *J Am Geriatr Soc*. 50(6): Supplement.
Knowles, S. (1993). Symptom management in palliative care. *On Continuing Practice*. 20(1): 20-25.

Geriatric Pharmacology

Beers MH (1997). Explicit criteria for determining potentially inappropriate medication use by the elderly. *Arch Intern Med*, 157:1531-1536.
Carlson JE (1996). Perils of polypharmacy: 10 steps to prudent prescribing. *Geriatrics*, 51(7):26-35.
Fick DM, Cooper JW, Wade WE, Waller JL, Maclean R, Beers MH (2003). Updating the Beers Criteria for potentially inappropriate medication use in older adults. *Arch Intern Med*, 163: 2716-2724.
Fordyce, M. (1999). *Geriatric Pearls*. Philadelphia: FA Davis Company.
Lewis, T. (2004) Using the NO TEARS tool for medication review. *BMJ*, 329(7463):434

Hannah Chiu, Roopan Gill, and Rebecca Menzies, chapter editors

Christopher Kitamura and Michelle Lam, associate editors

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Dr. Jason Dodge and Dr. Sari Kives, staff editors

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Basic Anatomy Review

A. EXTERNAL GENITALIA (Figure 1)

- referred to collectively as the vulva
- blood supply: internal pudendal artery
- sensory innervation: pudendal nerve
- lymphatic drainage: inguinal nodes

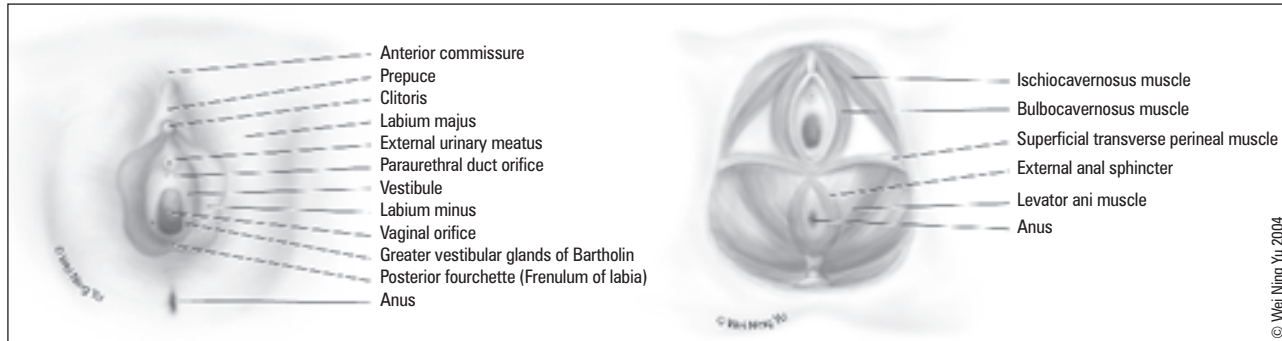


Figure 1. Vulva and Perineum

B. VAGINA

- muscular canal extending from cervix to vulva, anterior to rectum and posterior to bladder
- lined by rugated, stratified-squamous epithelium
- upper vagina separated by cervix into anterior, posterior and lateral fornices
- blood supply: vaginal branch of internal pudendal artery with anastomoses from uterine, inferior vesical and middle rectal arteries

C. UTERUS

- thick walled, muscular organ between bladder and rectum, consisting of two major parts:
 - uterine corpus
 - ♦ blood supply: uterine artery (branch of the internal iliac artery)
 - cervix
 - ♦ blood supply: cervical branch of uterine artery
- position (Figure 2)
 - anteverted (majority)
 - retroverted
- supported by the pelvic diaphragm, the pelvic organs and 4 paired sets of ligaments
 - round ligaments: travel from anterior surface of uterus, through broad ligaments, through inguinal canals then terminate in the labia majora
 - ♦ function: anteversion
 - ♦ blood supply: Sampson's artery (branch of uterine artery running through round ligament)
 - uterosacral ligaments: arise from sacral fascia and insert into posterior inferior uterus
 - ♦ function: mechanical support for uterus and contain autonomic nerve fibres
 - cardinal ligaments: extend from lateral pelvic walls and insert into lateral cervix and vagina
 - ♦ function: mechanical support, prevents prolapse
 - broad ligaments: pass from lateral pelvic wall to sides of uterus; contains fallopian tube, round ligament, ovarian ligament, nerves, vessels and lymphatics
- infundibulopelvic ligament: continuous tissue that connects ovary to pelvic wall
 - contains the ovarian artery, ovarian vein, ovarian plexus, lymphatic vessels



Anteversion: forward tilted uterus

Anteflexion: bending of uterus so the fundus is thrust forward

Retroversion: backward tilted uterus

Retroflexion: bending of uterus so the fundus is thrust backward

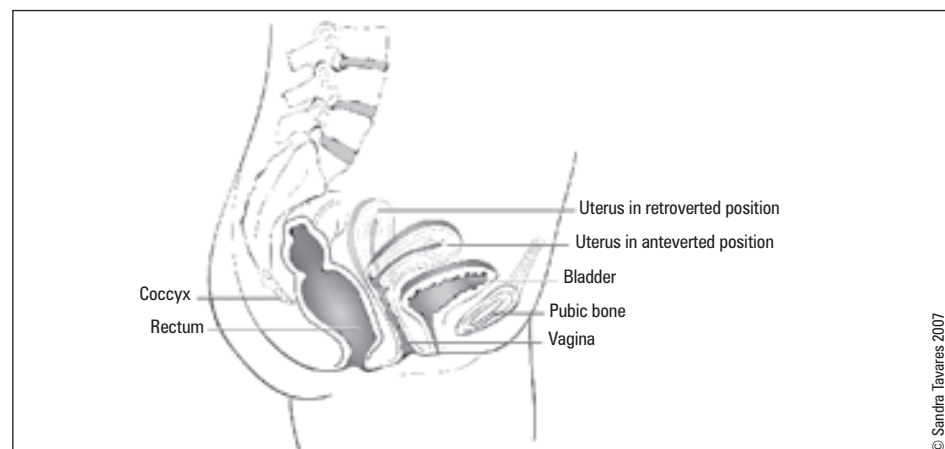


Figure 2. Positioning of Uterus

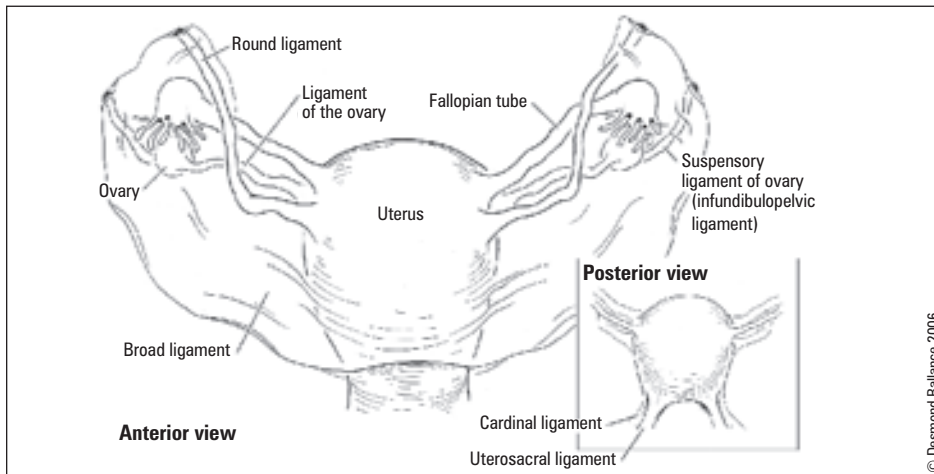


Figure 3. Internal Genital Organs

D. FALLOPIAN TUBES

- 8-14 cm muscular tubes extending laterally from the uterus to ovary
- interstitial, isthmic, ampullary and infundibular segments; terminates at fimbriae
- mesosalpinx: peritoneal fold that attaches fallopian tube to broad ligament
- blood supply: uterine and ovarian arteries

E. OVARIES

- consist of cortex with ova and medulla with blood supply
- supported by infundibulopelvic ligament (suspensory ligament of ovary)
- mesovarium: peritoneal fold that attaches ovary to broad ligament
- blood supply: ovarian arteries (branches off aorta), left ovarian vein (drains into left renal vein), right ovarian vein (drains into inferior vena cava)

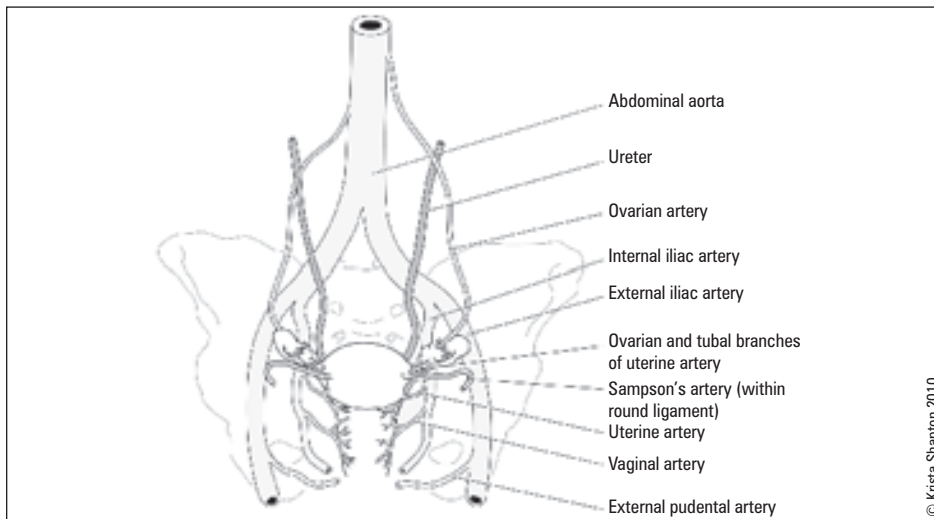


Figure 4. Vascular Supply

Menstruation

Stages of Puberty

- see Pediatrics, P17
- adrenarche: increase in secretion of adrenal androgens; usually precedes gonadarche by 2 years
- gonadarche: increased secretion of gonadal sex steroids; ~age 8
- thelarche: breast development
- pubarche: pubic and axillary hair development
- menarche: onset of menses, usually following peak height velocity and/or 2 years following breast budding



The ureters run posterior to the uterine arteries
Water under the bridge



Stages of Puberty
Boobs, Pubes, Grow, Flow
"Thelarche, Pubarche, Growth spurt, Menarche"



Tanner Stage
Thelarche
I. None
II. Breast bud
III. Further enlargement of areola and breasts with no separation of their contours
IV. 2nd mound of areola and papilla
V. Areola recessed to general contour of breast = adult

Pubarche
I. None
II. Downy hair along labia only
III. Darker/coarse hair extends over pubis
IV. Adult type covers smaller area, no thigh involvement
V. Adult hair in quantity and type and extends over thighs

Menstrual Cycle

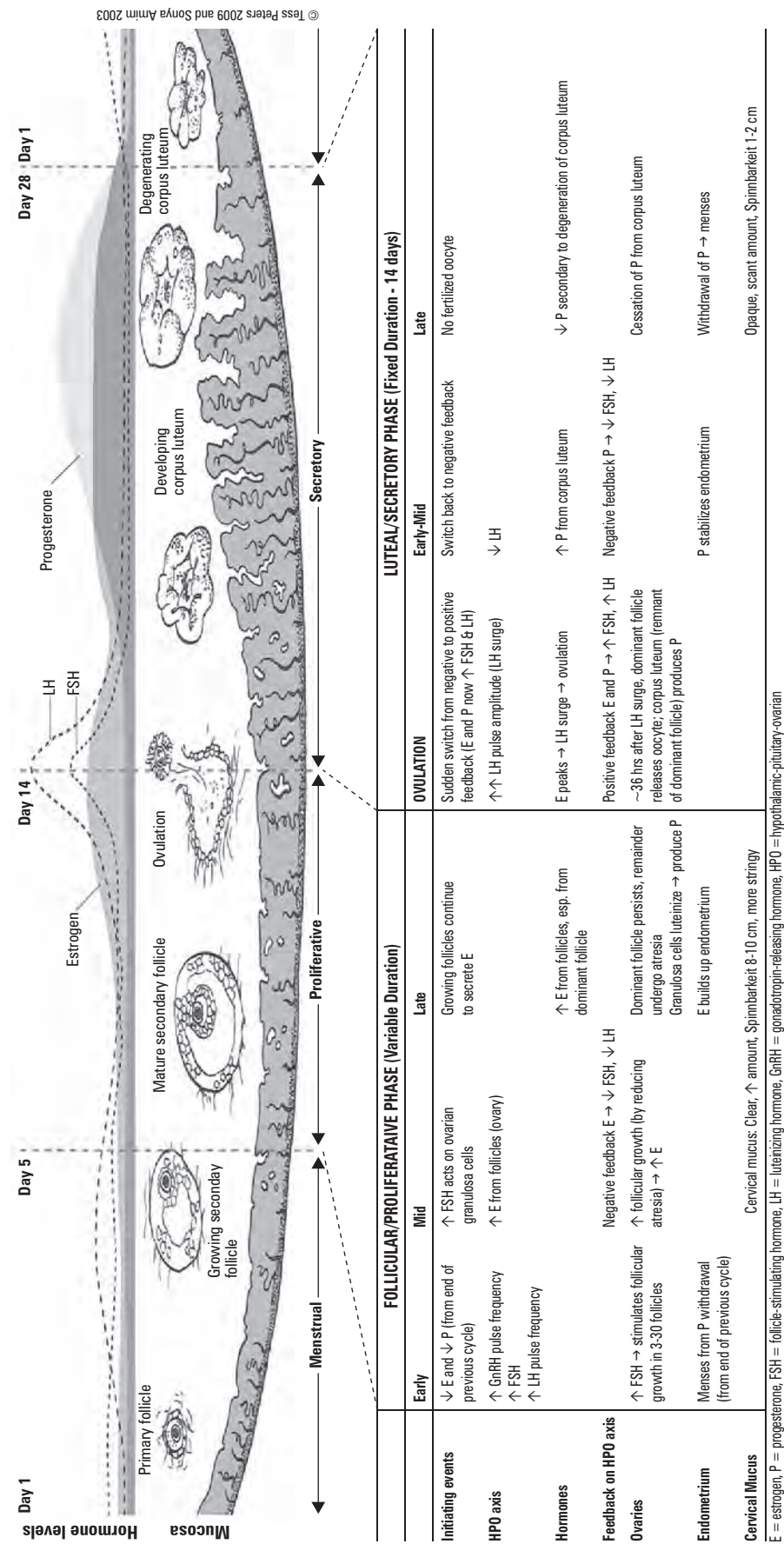


Figure 5. Events of the Normal Menstrual Cycle

Characteristics

- Menarche 10-15 years
- Average 12.2 years
- Entire cycle 28 ± 7 days with bleeding for 1-6 days
- 25-80 mL blood loss per cycle

Estrogen

ESTROGEN is the main hormone in the follicular/proliferative phase. Stimulated by LH. Estrogen mainly decreases FSH. The majority of estrogen is secreted by the dominant follicle.

Estrogen effects:

- On the follicles in the ovaries:
 - Reduces atresia
- On the endometrium:
 - Proliferation of glandular and stromal tissue
- On all target tissues:
 - Decreases E receptors

Progesterone

PROGESTERONE is the main hormone in the luteal/secretory phase stimulated by LH. Progesterone mainly decreases LH and is secreted by the corpus luteum (remnant of dominant follicle).

Progesterone effects:

- On the endometrium:
 - cessation of mitoses (stops building endometrium up)
 - "organization" of glands (initiates secretions from glands)
 - inhibits macrophages, interleukin-8 and enzymes from degrading endometrium
- On all target tissues:
 - decreased E receptors (the "anti-estrogen" effect)
 - decreased P receptors

Premenstrual Syndrome (PMS)

- synonyms: “ovarian cycle syndrome,” “menstrual molimina” (moodiness)

Etiology

- not completely understood, multifactorial, genetics likely play a role
- CNS-mediated neurotransmitter interactions with sex steroids (progesterone, estrogen and testosterone)
- serotonergic dysregulation – currently most plausible theory

Diagnostic Criteria for Premenstrual Syndrome

- at least one of the following affective and somatic symptoms during the 5 days before menses in each of the three prior menstrual cycles
 - affective: depression, angry outbursts, irritability, anxiety, confusion, social withdrawal
 - somatic: breast tenderness, abdominal bloating, headache, swelling of extremities
- symptoms relieved within 4 days of onset of menses
- symptoms present in the absence of any pharmacologic therapy, drug or alcohol use
- symptoms occur reproducibly during 2 cycles of prospective recording
- patient suffers from identifiable dysfunction in social or economic performance

Treatment

- goal: symptom relief
- psychological support
- diet/supplements
 - avoid sodium, simple sugars, caffeine and alcohol
 - calcium (1200-1600 mg/d), magnesium (400-800 mg/d), vitamin E (400 IU/d), vitamin B₆
- medications
 - NSAIDs for discomfort, pain
 - spironolactone for fluid retention: used during luteal phase
 - SSRI antidepressants: used during luteal phase x 14 days or continuously
 - progesterone suppositories
 - OCP: primarily beneficial for physical/somatic symptoms
 - danazol: an androgen that inhibits pituitary-ovarian axis
 - GnRH agonists if severe PMS unresponsive to other treatment
- mind/body approaches
 - regular aerobic exercise
 - cognitive behavioural therapy
 - relaxation, light therapy biofeedback and guided imagery
- herbal remedies (variable evidence)
 - evening primrose oil, black cohosh, St. John's wort, kava, ginkgo



Premenstrual Syndrome

Physiological and emotional disturbances which generally occur 1-2 weeks preceding menses until a few days after onset of menses. Common symptoms include depression, irritability, tearfulness and mood swings.

Premenstrual Dysphoric Disorder (PMDD)

Definition

- official diagnosis in the DSM-IV-TR
- described as a more severe form of PMS with specific diagnostic criteria
- treatment with SSRIs (first line), and Yaz® OCP (highly effective)
- see [Psychiatry](#), PS11

Differential Diagnoses of Common Presentations



Abnormal Uterine Bleeding (AUB)

- see *Disorders of Menstruation*, GY13
- definition: change in frequency, duration or amount of menstrual flow
- classified as amenorrhea, oligomenorrhea, menorrhagia/hyperménorrhagia, hypomenorrhea, metrorrhagia, menometrorrhagia, polymenorrhea, postmenopausal bleeding
 - hypomenorrhea: bleeding that is decreased in amount
 - polymenorrhea: bleeding occurring at intervals <21 days
 - menorrhagia/hyperménorrhagia: bleeding at regular intervals that is prolonged in duration (>7 days) or excessive in amount (>80 cc per menstrual cycle)
 - metrorrhagia: bleeding at irregular intervals, particularly between expected menstrual periods
 - menometrorrhagia: excessive bleeding at usual time of menstrual periods and at other irregular intervals
 - postmenopausal bleeding: any bleeding that presents >1 year after menopause; endometrial cancer until proven otherwise



Dysmenorrhea

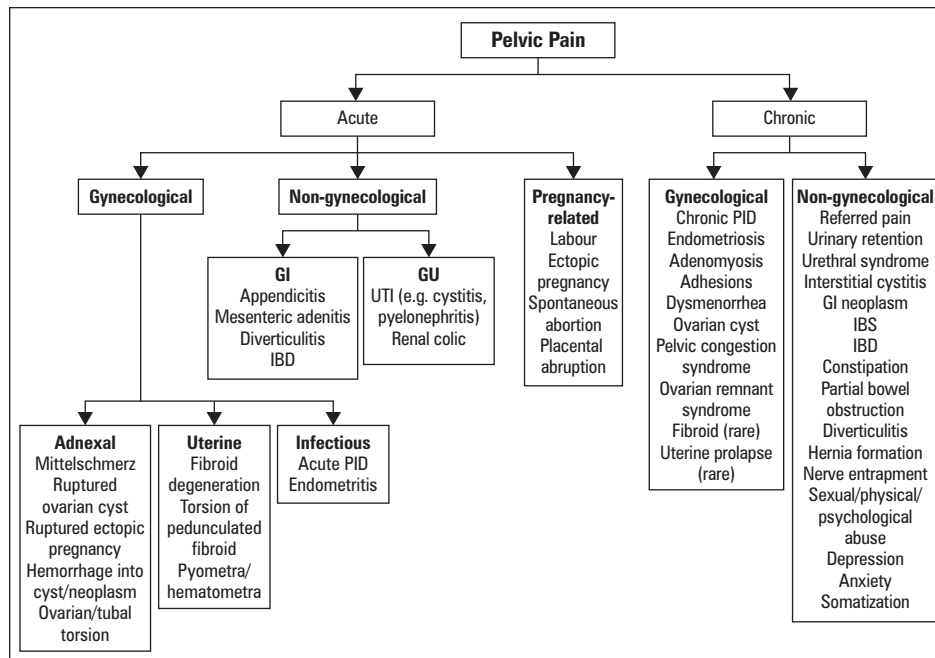
Dysmenorrhea
Painful menstruation.

- see *Disorders of Menstruation*, GY12
- primary/idiopathic
- secondary (acquired)
 - endometriosis
 - adenomyosis
 - uterine polyps
 - uterine anomalies (e.g. non-communicating uterine horn)
 - leiomyoma
 - intrauterine synechiae
 - ovarian cysts
 - cervical stenosis
 - imperforate hymen, transverse vaginal septum
 - pelvic inflammatory disease (PID)
 - IUD – copper
 - foreign body

Vaginal Discharge/Pruritus

- see *Gynecological Infections*, GY24
- physiologic discharge and cervical mucus production
- non-physiologic
 - genital tract infection
 - vulvovaginitis: candidiasis, trichomoniasis, bacterial vaginosis (BV), polymicrobial superficial infection
 - chlamydia, gonorrhea
 - pyosalpinx, salpingitis
 - genital tract inflammation (non-infectious)
 - local: chemical irritants, douches, sprays, foreign body, trauma, atrophic vaginitis, desquamative inflammatory vaginitis, focal vulvitis
 - neoplasia: vulvar, vaginal, cervical, endometrial
 - systemic: toxic shock syndrome, Crohn's disease, collagen disease, dermatologic (e.g. lichen sclerosis)
 - IUD, OCP (secondary to progesterone)

Pelvic Pain



Chronic Pelvic Pain (CPP)
Intermittent or constant pain of
> 6 months duration.

20% of CPP patients have a history of
previous sexual abuse/assault.
(remember to ask about it!)

Pyometra
Pus within the uterine cavity.

Hematometra
Blood within the uterine cavity.

Figure 6. Approach to Pelvic Pain

Pelvic Mass

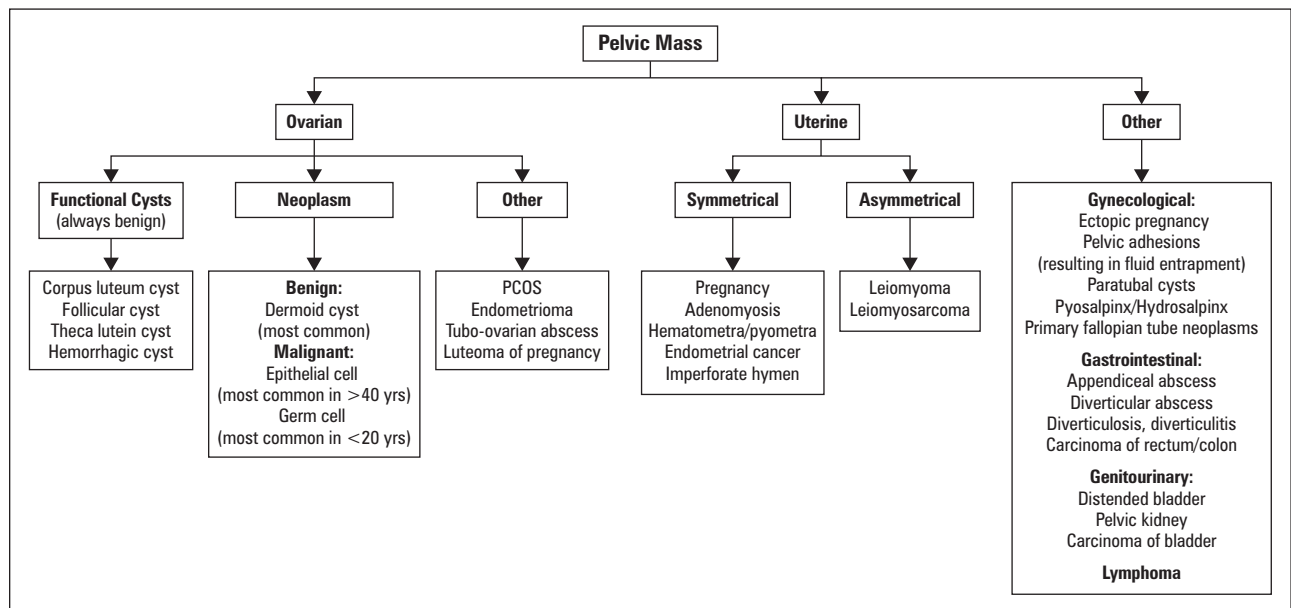


Figure 7. Differential Diagnosis of Pelvic Mass



Dyspareunia

Dyspareunia
Painful intercourse.

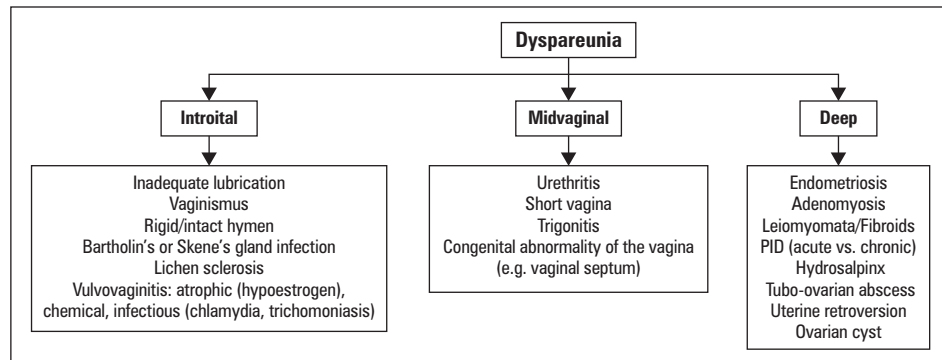


Figure 8. Approach to Dyspareunia

Common Investigations

Bloodwork

- CBC
 - evaluation of severity of abnormal uterine bleeding, pre-op investigation \pm ferritin if anemic
- beta-hCG
 - investigation of possible pregnancy, ectopic pregnancy, ovarian germ cell tumour
 - work-up for gestational trophoblastic disease/neoplasia (GTD/GTN)
 - monitored after medical management of ectopic pregnancy and GTN to assess for cure or recurrence
- LH, FSH, TSH, free T_4 , PRL, DHEA, testosterone, estradiol, androstenedione
 - investigation of amenorrhea, menstrual irregularities, menopause, infertility

Imaging

Ultrasound (U/S)

- transabdominal or transvaginal U/S is imaging modality of choice for pelvic structures
- transvaginal U/S provides better resolution of uterus and adnexal structures
 - detects early pregnancy if beta-hCG ≥ 1500 (beta-hCG must be ≥ 6500 for transabdominal U/S)
- may be used to identify pelvic pathology
 - identify ectopic pregnancy, intrauterine pregnancy
 - assess uterine, adnexal, cul-de-sac, ovarian masses (e.g. solid or cystic)
 - determine endometrial thickness, locate/characterize fibroids
 - monitor follicles during assisted reproduction

Sonohysterography (SHG)

- saline infusion into endometrial cavity expands endometrial cavity, improving visualization of uterus and fallopian tubes
- useful for investigation of
 - abnormal uterine bleeding (AUB)
 - uncertain endometrial findings on transvaginal U/S
 - infertility (tubal patency)
 - congenital/acquired uterine abnormalities (e.g. fibroids, endometrial polyps)
- easily done, minimal cost, well-tolerated, sensitive and specific
- frequently avoids need for diagnostic hysteroscopy

Hysterosalpingography (HSG)

- x-ray contrast introduced through the cervix into the uterus
- used for evaluation of size, shape, configuration of uterus, congenital uterine abnormalities, tubal patency, or obstruction
- useful for investigation of infertility



Check for STIs before performing SHG and HSG to prevent PID in high-risk individuals.

Common Procedures

Genital Tract Biopsy

Vulvar Biopsy

- performed under local anesthetic
- Keyes/punch biopsy
- hemostasis achieved with local pressure and Monsel's solution (ferric sulfate), silver nitrate or suture (rarely)

Vaginal Biopsy and Cervical Biopsy

- anesthetic not necessary
- punch biopsy or biopsy forceps
- hemostasis with Monsel's solution and pressure

Endometrial Biopsy

- performed in the office using an endometrial suction curette (pipelle) guided through the cervix to aspirate fragments of endometrium
 - pre-treatment with misoprostol (Cytotec®) if nulliparous or postmenopausal
- more invasive procedure (D&C) may be done in the office or operating room ± hysteroscopy

Colposcopy



- **diagnostic use**
 - magnifies surface structures of the vulva, vagina, cervix and perianal region
 - 1% acetic acid wash applied to cervix dehydrates cells and reveals "acetowhite" areas that correspond to increased nucleus-to-cytoplasm ratio (abnormal)
 - allows biopsy of acetowhite lesions for early identification of dysplasia and cancer
- **therapeutic use**
 - cryotherapy: nitrous oxide or carbon dioxide freezes dysplastic lesions, genital warts
 - laser vaporization: used to treat dysplastic lesions of the exocervix and benign ectropion
 - loop electrosurgical excision procedure (LEEP): excision of transformation zone with the cervical lesion; provides a specimen for pathological examination

Dilatation and Curettage (D&C)

- prior to procedure, determine depth with uterine sound
- dilatation of cervix with dilators of increasing diameter
- scrape entire uterine cavity with sharp curette
- anesthesia: general or local

Indications

- diagnostic (rarely done without hysteroscopy)
 - abnormal uterine bleeding (AUB)
 - dysfunctional uterine bleeding (DUB)
- therapeutic
 - removal of retained products of conception following abortion
 - termination of pregnancy in 1st trimester
 - removal of small uterine polyps or pedunculated submucosal fibroids

Complications

- bleeding
- infection
- perforation of uterus, laceration of cervix
 - reduce risk with preoperative misoprostol (Cytotec®) inserted per vagina to soften cervix and stimulate uterine contraction
- incompetent cervix – extremely rare

Laparoscopy

- laparoscope (fiber optic camera) used to view pelvic/abdominal contents through small incisions

Indications

- diagnostic
 - evaluation of infertility, pelvic pain, pelvic masses, congenital anomalies, hemoperitoneum and endometriosis
- therapeutic
 - tubal ligation
 - lysis of adhesions
 - excision of ectopic pregnancy
 - excision/ablation of endometriosis
 - retrieval of lost IUDs
 - cystectomy, salpingo-oophorectomy and hysterectomy
 - myomectomy
 - treatment of stress urinary incontinence

Contraindications

- bowel obstruction
- large hemoperitoneum
- clinically unstable patient
- inability to maintain pneumoperitoneum
- multiple previous abdominal surgeries (i.e. adhesions)

Complications

- general anesthetic
- insufflation of the preperitoneal abdominal wall
- injury to vascular structures (e.g. aorta, inferior epigastric vessels)
- injury to viscous (bowel, bladder, ureters)
- may need to convert to laparotomy
- infection

Hysteroscopy

- flexible or rigid scope inserted through cervix into uterus to visualize uterine cavity
- distension medium is used to allow inspection of this potential space

Indications

- diagnostic
 - detection of uterine anomalies or pathology (e.g. infertility work-up)
 - AUB
 - DUB
- therapeutic
 - removal of uterine polyps, fibroids, adhesions, septums
 - endometrial ablation

Complications

- perforation of uterus, laceration of cervix
- bleeding
- infection
- absorption of excess distension medium (when sugar solutions utilized)
 - fluid overload, hyponatremia
 - procedure should be abandoned if the fluid deficit rises to 1L; consider stopping at 500 cc
- air emboli
- anaphylactic shock

Endometrial Ablation

- alternative invasive procedure to hysterectomy for treatment of AUB; performed as outpatient
- rationale is to coagulate or resect the endometrium basalis layer to prevent monthly build-up and reduce menstrual losses

Methods

- rollerball electrode coagulation or resection
- microwave endometrial ablation
- thermoablation (hot water), balloon ablation
- laser photocoagulation

Complications

- infection
- injury to pelvic viscera if perforated uterus
- hematometra
- absorption of excess distention medium → fluid overload, hyponatremia
- failure (i.e. bleeding/menorrhagia persists)
- may eventually require hysterectomy for recurrence of symptoms (~20% at 5 years)

Hysterectomy

Indications

- uterine fibroids
- endometriosis, adenomyosis
- uterine prolapse
- pelvic pain
- AUB
- cancer (endometrium, ovaries, fallopian tubes, cervical)

Complications

- general anesthetic
- bleeding
- infection
- injury to other organs (ureter, bladder, rectum)
- loss of ovarian function (if ovaries removed, iatrogenic menopause)

Approaches

1. vaginal vs. abdominal
 - indications for vaginal approach: mobile uterus, uterine size <12 weeks
 - advantages of vaginal approach: less pain, faster recovery time, allows for simultaneous repair of rectocele/cystocele/enterocele, improved esthetics
2. open vs. laparoscopic-assisted
 - advantages of laparoscopy: less pain, faster recovery, improved esthetics, shorter hospital stay



Approaches to Hysterectomy

Abdominal hysterectomy: uterus removed via transverse or vertical laparotomy.

Vaginal hysterectomy: uterus removed via vagina. No visualization or entry into abdomen unless laparoscopic-assisted.

Table 1. Classification of Hysterectomy

Classification	Tissues Removed	Indications
Subtotal hysterectomy	Uterus	Inaccessible cervix (e.g. adhesions) Patient choice/preference
Total hysterectomy	Uterus, cervix	Uterine fibroids Endometriosis Adenomyosis Menorrhagia DUB
Total hysterectomy + bilateral salpingo-oophorectomy (TH/BSO)	Uterus, cervix, fallopian tubes, ovaries	Endometrial cancer Benign or malignant adnexal masses >45 years old Consider for endometriosis
Radical hysterectomy	Uterus, cervix, fallopian tubes, ovaries, broad ligaments, parametria, upper half of vagina, regional lymph nodes	Cervical cancer (up to stage IBI, see Table 17)



Disorders of Menstruation

Amenorrhea

Primary Amenorrhea

No menses by age 14 in absence of 2° sexual characteristics or no menses by age 16 with 2° sexual characteristics.

Secondary Amenorrhea

No menses for >6 months or 3 cycles after documented menarche.

Oligomenorrhea

Episodic vaginal bleeding occurring at intervals >35 days.



2° amenorrhea is pregnancy until proven otherwise.



Prolactinoma Symptoms

Galactorrhea, visual changes, headache.

Etiology

- see *Differential Diagnoses of Common Presentations*, GY6

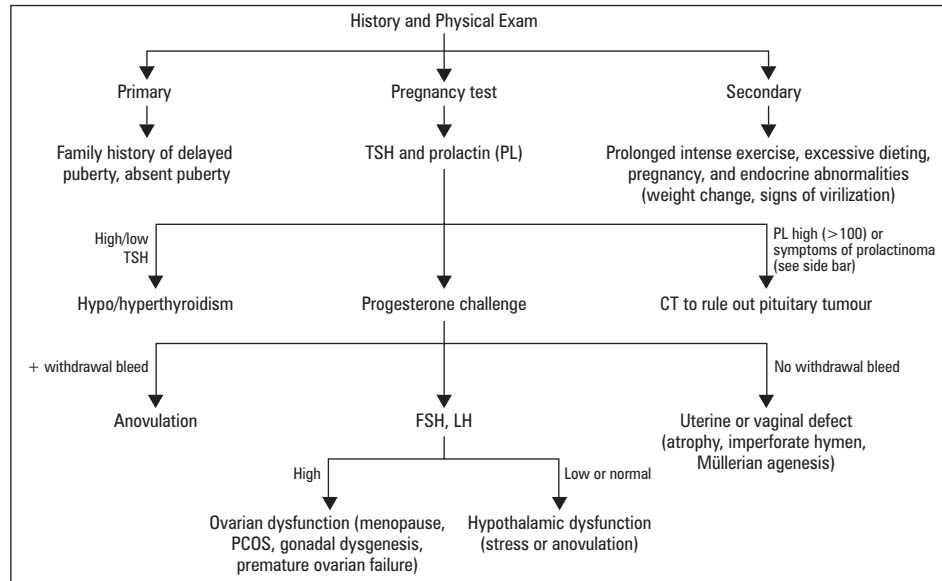


Figure 9. Diagnostic Approach to Amenorrhea

Investigations (see Figure 9)

- beta-hCG, hormonal workup (TSH, prolactin, FSH, LH, androgens, estradiol)
- progesterone challenge to assess estrogen status
 - medroxyprogesterone acetate (Provera®) 10 mg PO OD for 10 days
 - any uterine bleed within 2-7 days after completion of Provera® is considered to be a positive test/withdrawal bleed
 - ♦ withdrawal bleed suggests presence of adequate estrogen to thicken the endometrium; thus withdrawal of progesterone results in bleeding
 - ♦ if no bleeding occurs, there may be inadequate estrogen (hypoestrogenism) or excessive androgens
- karyotype if indicated (if premature ovarian failure or absent puberty)
- U/S to confirm normal anatomy, identify PCOS

Treatment

- **hypothalamic dysfunction (low or normal FSH, LH)**
 - if low FSH/LH, consider head imaging (CT or MRI) if no other obvious etiology
 - stop any medications, reduce stress, adequate nutrition, decrease excessive exercise
 - if pregnancy desired, correct underlying problem; but may require gonadotropins to stimulate ovulation
 - otherwise OCP to induce menstruation (withdrawal bleed) – may not prevent other manifestations of hypoestrogenic state, e.g. bone loss
- **hyperprolactinemia**
 - consider CT of head to document presence of pituitary micro/macroadenoma
 - surgery for macroadenoma (rarely)
 - bromocriptine if fertility desired; OCP if fertility not desired
- **premature ovarian failure (high FSH, LH)**
 - karyotype
 - removal of gonadal tissue if Y chromosome present (at 18 years or earlier if dysgenic gonads)
 - HRT or OCP to prevent manifestations of hypoestrogenic state
- treat associated autoimmune disorders (thyroid, adrenal)
- **PCOS**
 - see *Polycystic Ovarian Syndrome*, GY23

Abnormal Uterine Bleeding (AUB)

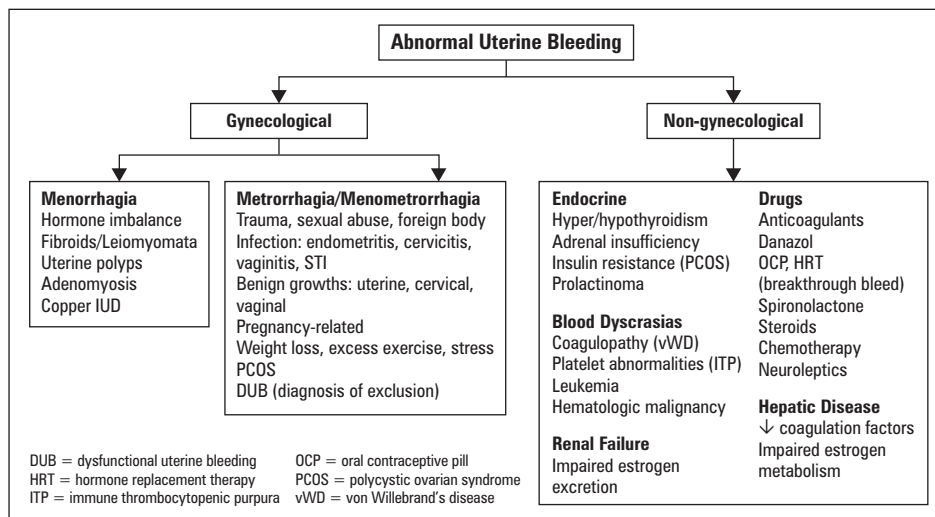


Figure 10. Approach to Abnormal Uterine Bleeding

Table 2. Comparison of Anovulatory and Ovulatory Abnormal Uterine Bleeding

	Anovulatory	Ovulatory
Incidence	90%	10%
Definition	Unpredictable endometrial bleeding of variable flow and duration; sex steroids are produced but not cyclically, resulting in irregular bleeding	Typically cyclic, but heavy or prolonged
Etiology	PCOS Thyroid dysfunction Elevated prolactin levels Rare estrogen-producing tumours Stress, weight loss, exercise Liver and kidney disease	Anatomic or physical lesion (e.g. polyp, fibroid, adenomyosis, neoplasm, foreign body) Hemostatic defect Infection; trauma Local disturbances in prostaglandins (elevated endometrial vasodilatory prostaglandins, decreased vasoconstrictive prostaglandin)
Pathophysiology	Estrogen dependent breakthrough bleeding: chronic estrogen production unopposed by adequate progesterone production → continued proliferation of the endometrium → thickened endometrium outgrows its blood supply → focal necrosis with partial shedding not uniformly → bleeding is usually irregular, prolonged, and heavy	Depends on underlying etiology

Investigations

- CBC, serum ferritin
- beta-hCG
- TSH, free T₄
- coagulation profile (esp. adolescent): rule out von Willebrand's disease
- prolactin if amenorrheic
- FSH, LH
- serum androgens (especially free testosterone)
- day 21 (luteal phase) progesterone to confirm ovulation
- Pap test
- pelvic U/S: detect polyps, fibroids; measure endometrial thickness (postmenopausal)
- SHG: very sensitive for intrauterine pathology (polyps, submucous fibroids)
- HSG
- endometrial biopsy: women >40 years are at higher risk of endometrial cancer
 - must do endometrial biopsy in **all** women presenting with postmenopausal bleeding to exclude endometrial cancer
- D&C: not for treatment; diagnosis only (usually with hysteroscopy)

Dysfunctional Uterine Bleeding

Abnormal bleeding not attributable to organic (anatomic/systemic) disease. DUB is a diagnosis of exclusion. Anovulatory AUB often used synonymously with DUB.

Treatment

- treat underlying disorders:
 - if anatomic lesions and systemic disease have been ruled out, consider dysfunctional uterine bleeding (DUB)
- medical
 - mild DUB (see sidebar)
 - ♦ NSAIDs
 - ♦ anti-fibrinolytic (e.g. Cyklokapron®) at time of menses
 - ♦ combined OCP
 - ♦ progestins (Provera®) on first 10-14 days of each month if oligomenorrheic
 - ♦ Mirena® IUD
 - ♦ danazol
 - acute, severe DUB
 - ♦ replace fluid losses, consider admission
 - ♦ medical treatment
 - a) estrogen (Premarin®) 25 mg IV q4h x 24h with Gravol® 50 mg IV/PO q4h or
 - b) Ovral® 1 tab PO q4h x 24h with Gravol® 50 mg IV/PO q4h
 - taper Ovral®: 1 tab tid x 2d → bid x 2d → OD
 - ♦ after (a) or (b), maintain patient on monophasic OCP for next several months or consider alternative medical treatment
 - clomiphene citrate
 - ♦ consider in patients who are anovulatory and who wish to get pregnant
- surgical
 - endometrial ablation; consider pretreatment with danazol or GnRH agonists
 - ♦ if finished childbearing
 - ♦ repeat procedure may be required if symptom recurrence
 - hysterectomy: definitive treatment



Dysmenorrhea

Etiology

- see *Differential Diagnoses of Common Presentations*, GY6

Table 3. Comparison of Primary and Secondary Dysmenorrhea

	Primary Dysmenorrhea	Secondary Dysmenorrhea
Features	Menstrual pain in absence of organic disease Begins 6 months-2 years after menarche (once ovulatory cycles established)	Menstrual pain due to organic disease Usually begins in women who are in their 20s, worsens with age May improve temporarily after childbirth
Signs and Symptoms	Colicky pain in abdomen, radiating to the lower back, labia, and inner thighs beginning hours before onset of bleeding and persisting for hours or days (48-72 h) Associated symptoms: nausea, vomiting, altered bowel habits, headaches, fatigue [prostaglandin (PG)-associated]	Associated dyspareunia, abnormal bleeding, infertility
Diagnosis	Associated dyspareunia, abnormal bleeding, infertility Rule out underlying pelvic pathology and confirm cyclic nature of pain	Bimanual exam: uterine or adnexal tenderness, fixed uterine retroflexion, uterosacral nodularity, pelvic mass, or enlarged irregular uterus U/S, laparoscopy and hysteroscopy may be necessary to establish the diagnosis
Treatment	PG synthetase inhibitors (e.g. Anaprox®) • Should be started before onset of pain OCP: suppress ovulation/reduce menstrual flow	Treat underlying cause

Primary Dysmenorrhea

Menstrual pain in absence of organic disease.

Secondary Dysmenorrhea

Menstrual pain due to organic disease.

Endometriosis



Etiology

- not fully understood
- proposed mechanisms (combination likely involved)
 - retrograde menstruation (Sampson's theory)
 - ♦ seeding of endometrial cells by transtubal regurgitation during menstruation
 - ♦ endometrial cells most often found in dependent sites of the pelvis
 - immunologic theory: altered immunity may limit clearance of transplanted endometrial cells from pelvic cavity (may be due to decreased NK cell activity)
 - metaplasia of coelomic epithelium
 - ♦ undefined endogenous biochemical factor may induce undifferentiated peritoneal cells to develop into endometrial tissue
 - extrapelvic disease may be due to aberrant vascular or lymphatic dissemination of cells
 - ♦ e.g. ovarian endometriosis may be due to direct lymphatic flow from uterus to ovaries

Epidemiology

- incidence: 15-30% of pre-menopausal women
- mean age at presentation: 25-30 years
- regresses after menopause

Risk Factors

- family history (7-10 fold increased risk if affected 1st degree relative)
- obstructive anomalies of the genital tract (earlier onset)
- nulliparity
- age >25 years

Sites of Occurrence

- ovaries: 60% patients have ovarian involvement
- broad ligament, vesicoperitoneal fold
- peritoneal surface of the cul-de-sac, uterosacral ligaments
- rectosigmoid colon, appendix
- rarely may occur in sites outside abdomen/pelvis, including lungs

Clinical Features

- may be asymptomatic
- history
 - menstrual symptoms
 - ♦ cyclic symptoms due to growth and bleeding of ectopic endometrium, usually precede menses (24-48 hrs) and continue throughout and after flow
 - ♦ secondary dysmenorrhea
 - ♦ sacral backache with menses
 - ♦ pain may eventually become chronic, worsening perimenstrually
 - ♦ premenstrual and postmenstrual spotting
 - ♦ deep dyspareunia
 - infertility
 - ♦ 30-40% of patients with endometriosis will be infertile
 - ♦ 15-30% of those who are infertile will have endometriosis
 - bowel and bladder symptoms
 - ♦ frequency, dysuria, hematuria
 - ♦ diarrhea, constipation, hematochezia, dyschezia
- physical
 - tender nodularity of uterine ligaments and cul-de-sac felt on rectovaginal exam
 - fixed retroversion of uterus
 - firm, fixed adnexal mass (endometrioma)
 - physical findings not present in adolescent population

Investigations

- definitive diagnosis requires:
 - direct visualization of lesions typical of endometriosis at laparoscopy
 - biopsy and histologic exam of specimens (2 or more of: endometrial epithelium, glands, stroma, hemosiderin-laden macrophages)
- laparoscopy
 - mulberry spots: dark blue or brownish-black implants on the uterosacral ligaments, cul-de-sac or anywhere in the pelvis
 - endometrioma: "chocolate" cysts on the ovaries
 - "powder-burn" lesions on the peritoneal surface
 - early white lesions and clear blebs
 - peritoneal "pockets"
- CA-125
 - may be elevated in patients with endometriosis

Endometriosis

The presence of endometrial tissue (glands and stroma) outside of the uterine cavity.



Differential Diagnosis

1. Chronic PID, recurrent acute salpingitis
2. Hemorrhagic corpus luteum
3. Benign/malignant ovarian neoplasm
4. Ectopic pregnancy



Endometrioma = endometriotic cyst on surface of ovary.



There may be little correlation between the extent of endometriosis and symptomatology.



Classic Triad of Endometriosis

- Dysmenorrhea
- Dyspareunia (cul de sac, uterosacral ligament)
- Dyschezia (uterosacral ligament, cul-de-sac, rectosigmoid attachment)



A sharp, firm, and exquisitely tender "barb" on the uterosacral ligament is a classic feature of endometriosis.



Endometriosis is classified according to a scoring system standardized by the American Society for Reproductive Medicine. Score is based on location and extent of disease.



Recurrence Rates
Medical therapy: 30-50%
Conservative surgery: 14-40%

Treatment

- depends on certainty of the diagnosis, severity of symptoms, extent of disease, desire for future fertility and impact to GI/GU systems (e.g. intestinal obstruction)
- **medical**
 - NSAIDs – e.g. naproxen sodium (Anaprox®)
 - pseudopregnancy
 - ♦ cyclic/continuous estrogen-progestin (OCP)
 - ♦ medroxyprogesterone (Depo-Provera®)
 - pseudomenopause
 - ♦ 2nd line: only short-term (<6 months) due to osteoporotic potential with prolonged use, unless add-back therapy (e.g. estrogen/progesterone or SERM)
 - ♦ danazol (Danocrine®) = weak androgen
 - side effects: weight gain, fluid retention, acne, hirsutism, voice change
 - ♦ leuprolide (Lupron®) = GnRH agonist (suppresses pituitary)
 - side effects: hot flashes, vaginal dryness, reduced libido
 - can use ≥12 months with add-back progestin or estrogen
- **surgical**
 - conservative laparoscopy using laser, electrocautery ± laparotomy
 - ♦ ablation/resection of implants, lysis of adhesions, ovarian cystectomy of endometriomas
 - definitive: bilateral salpingo-oophorectomy ± hysterectomy
 - ± follow-up with medical treatment for pain control NOT shown to impact on preservation of fertility
 - best time to become pregnant is immediately after conservative surgery



Adenomyosis

Adenomyosis

Extension of areas of endometrial glands and stroma into the myometrium.

- synonym: “endometriosis interna” (uterine wall may be diffusely involved)

Epidemiology

- 15% of females >35 years old; found in 20-40% of hysterectomy specimens
- mean age at presentation: 40-50 years old (older age group than seen in endometriosis)
- adenomyosis is a common histologic finding in asymptomatic patients

Clinical Features

- often asymptomatic
- menorrhagia, secondary dysmenorrhea, pelvic discomfort
- dyspareunia, dyschezia
- uterus symmetrically bulky, usually <14 cm, mobility not restricted, no associated adnexal pathology
- Halban sign: tender, softened uterus on premenstrual bimanual exam

Investigations

- clinical diagnosis
- U/S or MRI can be helpful
- endometrial sampling to rule out other pathology

Treatment

- iron supplements as necessary
- analgesics, NSAIDs
- OCP, Depo-Provera® (medroxyprogesterone)
- low dose danazol 100-200 mg PO OD (trial x 4 months)
- GnRH agonists (e.g. leuprolide)
- definitive: hysterectomy (no conservative surgical treatment)



Leiomyomata (Fibroids)

Leiomyomata/Fibroids

Benign smooth muscle tumour of the uterus (most common gynecological tumour).

Epidemiology

- diagnosed in approximately 40-50% of reproductive age women >35 years
- more common, larger and occur at earlier age in black women
- common indication for major surgery in females
- minimal malignant potential (1:1000)
- typically regress after menopause; enlarging fibroids in a postmenopausal woman should prompt consideration of malignancy

Pathogenesis

- estrogen stimulates monoclonal smooth muscle proliferation; progesterone stimulates production of proteins that inhibit apoptosis
- degenerative changes (occur when tumour outgrows blood supply)
 - hyaline degeneration (most common degenerative change)
 - cystic degeneration (from breakdown of hyaline)
 - red/carneous degeneration (hemorrhage into tumour, may occur in pregnancy)
 - fatty degeneration
 - calcification
 - sarcomatous degeneration (rare)
 - parasitic myoma: tumour becomes attached to another organ (typically omentum or small bowel mesentery), develops new blood supply and loses connection to uterus

Clinical Features

- majority asymptomatic (60%), often discovered as incidental finding on pelvic exam or U/S
- abnormal uterine bleeding (30%): dysmenorrhea, menorrhagia
- pressure/bulk symptoms (20-50%)
 - pelvic pressure/heaviness
 - increased abdominal girth
 - urinary frequency and urgency
 - acute urinary retention (extremely rare but surgical emergency!)
 - constipation, bloating (rare)
- acute pelvic pain
 - fibroid degeneration
 - fibroid torsion (pedunculated subserosal)
- infertility (submucosal), recurrent pregnancy loss
- pregnancy complications (potential enlargement and increased pain, obstructed labour, difficult C-section)

Investigations

- bimanual exam: uterus asymmetrically enlarged, usually mobile
- CBC: anemia
- ultrasound: to confirm diagnosis and assess location of fibroids
- sonohysterogram: useful for differentiating endometrial polyps from submucosal fibroids
- endometrial biopsy to rule out uterine cancer for abnormal uterine bleeding (especially if age >40 years)
- occasionally MRI is used for pre-op planning (e.g. before myomectomy)

Treatment

- only if symptomatic, rapidly enlarging or menorrhagia
- treat anemia if present
- conservative approach (watch and wait)
 - symptoms absent or minimal
 - fibroids <6-8 cm or stable in size
 - not submucosal (submucosal fibroids are more likely to be symptomatic)
 - currently pregnant due to increased risk of bleeding (follow-up U/S if symptoms progress)
- medical approach
 - antiprostaglandins (ibuprofen, other NSAIDs)
 - tranexamic acid (Cyklokapron®)
 - OCP/Depo-Provera®
 - GnRH agonist: leuprolide (Lupron®), danazol (Danocrine®)
 - short-term use only (6 months)
 - often used pre-myomectomy or pre-hysterectomy to reduce fibroid size
- interventional radiology approach
 - uterine artery embolization occludes both uterine arteries → shrinks fibroids by 50% at 6 months; improves menorrhagia in 90% of patients within 1-2 months; not an option in women considering childbearing
- surgical approach
 - myomectomy (hysteroscopic, transabdominal or laparoscopic): preserves fertility
 - endometrial resection of fibroid and endometrial ablation for menorrhagia
 - hysterectomy (see GY11)
 - note:** avoid operating on fibroids during pregnancy (due to ++ vascularity and potential pregnancy loss); expectant management usually best

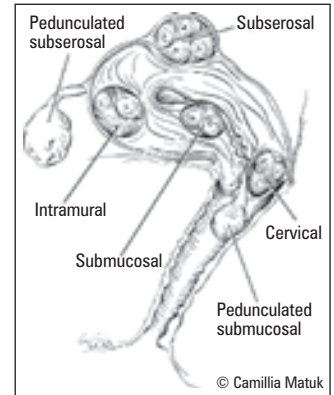


Figure 11. Possible Anatomic Locations of Uterine Leiomyomata



Submucosal leiomyomata are most symptomatic (bleeding, infertility).



Even with known fibroids, abnormal uterine bleeding + age >40 yrs – always do endometrial biopsy to rule out cancer.



Contraception

- see [Family Medicine](#), FM19

Table 4. Classification of Contraceptive Methods

Type	Effectiveness (perfect use, typical use)
Physiological	
Withdrawal/coitus interruptus	77.0%
Rhythm method/calendar/mucous/symptothermal	98.0%, 76.0%
Lactational amenorrhea	98% (first 6 months postpartum)
Chance – no method used	10.0%
Abstinence of all sexual activity	100.0%
Barrier Methods	
Condom alone	98.0%, 85.0%
Spermicide alone	82.0%, 71.0%
Sponge – Parous	80.0%, 68.0%
– Nulliparous	91.0%, 84.0%
Diaphragm with spermicide	94.0%, 84.0%
Female condom	95.0%, 79.0%
Cervical cap – Parous	74.0%, 68.0%
– Nulliparous	91.0%, 84.0%
Hormonal	
OCP	99.7%, 92.0%
Nuvaring	99.7%, 92.0%
Transdermal (Ortho Evra®)	99.7%, 92.0%
Depo-Provera®	99.7%, 97.0%
Progestin-only pill (Micronor®)	90-99%
Mirena® IUD	99.9%
Copper IUD	99.3%
Surgical	
Tubal ligation	99.65%
Vasectomy	99.9%
Emergency Postcoital Contraception (EPC)	
Yuzpe method	98% (within 24 hours)
“Plan B” levonorgestrel only	98% (within 24 hours)
Postcoital IUD	99.9%

Effectiveness: percentage of women reporting no pregnancy after 1 year of use.

Hormonal Methods

Combined Oral Contraceptive Pills (OCP)

- most contain low dose ethinyl estradiol (20-35 µg) plus progestin (norethindrone, norgestrel, levonorgestrel, desogestrel, norgestimate, drospirenone)
- failure rate (0.3% to 8%) depending on compliance
- monophasic or triphasic formulations (varying amount of progestin throughout cycle)

Transdermal (Ortho Evra®)

- continuous release of 6 mg norelgestromin and 0.60 mg ethinyl estradiol into bloodstream
- applied to lower abdomen, back, upper arm, buttocks, NOT breast
- worn for 3 consecutive weeks (changed every week) with 1 week off to allow menstruation
- as effective as OCP in preventing pregnancy (>99% with perfect use)
- may be less effective in women >90 kg body weight
- may not be covered by drug plans

Contraceptive Ring (Nuvaring®)

- thin flexible plastic ring; releases etonogestrel 120 µg/d and estradiol 15 µg/d
- works for 3 weeks then removed for 1 week to allow menstruation
- as effective as OCP in preventing pregnancy (98%)
- avoids first pass effect
- side effects: vaginal infection/irritation, vaginal discharge
- may have better cycle control, i.e. decreased breakthrough bleeding

Starting Hormonal Contraceptives

- thorough history and physical examination including blood pressure and breast exam
- follow-up visit 6 weeks after hormonal contraceptives prescribed
- pelvic exam can be delayed until a subsequent visit



Counselling the Adolescent about Contraception

More than 90% of adolescent pregnancies are unintended and approximately 50% of all pregnancies occur within the first 6 months of initiating sexual activity. In addition, 85% of sexually active women become pregnant within 1 year if no contraception is used and even some of the least effective contraceptive methods markedly decrease the risk of pregnancy.

Rimsza, ME. Counselling the Adolescent about Contraception. *Pediatr Rev* 2003; 24:162.

Risk of Thromboembolism in Women Taking Ethinylestradiol/Drospirenone and Other Oral Contraceptives.

Obstet Gynecol 2007; 110(3):587-93.

Purpose: To compare the association between thromboembolism and the use of ethinylestradiol/drospirenone (ie. Yasmin) or other oral contraceptives.

Study: Cohort study used a health insurer database and followed patients for an average of 7.6 months.

Patients: 22,429 women who had initiated ethinylestradiol/drospirenone were matched to 44,858 who had initiated other oral contraceptives between the age of 10 and 59 years.

Main Outcome: Thromboembolic events.

Results: The incidence rate of thromboembolism was similar between women initiating ethinylestradiol/drospirenone (1.3 per 1000 woman-years) compared to initiating other OCPs (1.4 per 1000 woman-years) (RR 0.9; 95% CI 0.5 – 1.6). Specific events, including deep vein thrombosis and pulmonary embolism also occurred with similar frequencies.

Summary: The risk of thromboembolism is similar in ethinylestradiol/drospirenone compared to other oral contraceptives.

Suppression of Ovarian Activity with a Drospirenone-Containing Oral Contraceptive in a 24/4 Regimen

Contraception 2008; 78:16-25

Study: Double-blind randomized.

Patients: Women aged 18-35 years post-ovulation or had a follicular diameter > 15 mm before day 23 during a pre-treatment cycle.

Intervention: Drospirenone 3mg plus ethinylestradiol 20 mcg administered in 24/4 regimen vs. 21/7 regimen.

Outcome: Suppression of ovarian activity (Hoogland score).

Results: Women on a 24/4 regimen had greater and more consistent ovarian suppression than the 21/7 group. 87.8% in the 24/4 group had no ovarian activity vs. 56% in the 21/7 group.



Irregular breakthrough bleeding often occurs in the first few months after starting OCP. Usually resolves after three cycles.

Table 5. Combined Estrogen and Progestin Contraceptive Methods

Mechanism of Action	Advantages	Side Effects	Contraindications
<ul style="list-style-type: none"> Ovulatory suppression through inhibition of LH and FSH Decidualization of endometrium Thickening of cervical mucus resulting in decreased sperm penetration 	<ul style="list-style-type: none"> Highly effective, reversible Cycle regulation Decreased dysmenorrhea and menorrhagia (less anemia) Decreased benign breast disease and ovarian cyst development Decreased risk of ovarian and endometrial cancer Increased cervical mucus which may lower risk of STIs Decreased PMS symptoms Improved acne Osteoporosis protection (possibly) 	<p>Estrogen-related</p> <ul style="list-style-type: none"> Nausea Breast changes (tenderness, enlargement) Fluid retention/bloating/edema Weight gain (rare) Migraine, headaches Thromboembolic events Liver adenoma (rare) Breakthrough bleeding (low estradiol levels) <p>Progestin-related</p> <ul style="list-style-type: none"> Amenorrhea/breakthrough bleeding Headaches Breast tenderness Increased appetite Decreased libido Mood changes Hypertension Acne/oily skin* Hirsutism* <p>* Androgenic side effects may be minimized by prescribing formulation containing desogestrel, norgestimate, drospirenone or cyproterone acetate</p>	<p>Absolute</p> <ul style="list-style-type: none"> Known/suspected pregnancy Undiagnosed abnormal vaginal bleeding Prior thromboembolic events, thromboembolic disorder (Factor V Leiden mutation; protein C, S or antithrombin III deficiency), active thrombophlebitis Cerebrovascular or coronary artery disease Estrogen-dependent tumours (breast, uterus) Impaired liver function associated with acute liver disease Congenital hypertriglyceridemia Smoker age >35 years Migraines with focal neurological symptoms (excluding aura) Uncontrolled hypertension <p>Relative</p> <ul style="list-style-type: none"> Migraines – non-focal with aura <1 hour Diabetes mellitus complicated by vascular disease SLE Controlled hypertension Hyperlipidemia Sickle cell anemia Gallbladder disease <p>Drug Interactions/Risks</p> <ul style="list-style-type: none"> Rifampin, phenobarbital, phenytoin and primidone can decrease efficacy, requiring use of back-up method No evidence of fetal abnormalities if conceived on OCP No evidence that OCP is harmful to nursing infant but may decrease milk production, not recommended until 6 weeks postpartum

Reference: World Health Organization Guidelines for Oral Contraceptive Pill (OCP) Use

Selected Examples of OCPs**Allesse®**

- 17 µg ethinyl estradiol and 0.5 mg lovonorgestrel
- low-dose therefore often a good starting OCP
- also used to help acne and to regulate menstrual cycles
- low-dose pills can often result in breakthrough bleeding; if this persists for longer than 3 months, patient should be switched to an OCP with higher estrogen content

Tri-cyclen®

- 35 µg ethinyl estradiol and 0.180 / 0.215 / 0.250 mg norgestimate
- triphasic oral contraceptive (graduated levels of progesterone)
- low androgenic activity can help with acne
- triphasic OCPs can not be used continuously (unlike monophasic formulations)

Yasmin® and Yaz®

- Yasmin®: 30 µg ethinyl estradiol + 3 mg drospirenone (a new progestin)
- Yaz®: 20 µg ethinyl estradiol + 3 mg drospirenone – 24/4-day pill (4 day pill free interval)
- drospirenone has antimineralocorticoid activity and antiandrogenic effects
- benefits: decreased perception of cyclic weight gain, bloating; fewer PMS symptoms; improved acne
- adverse effects: hyperkalemia (rare, contraindicated in renal and adrenal insufficiency)
- check potassium if patient also on ACE inhibitor, ARB, K-sparing diuretic, heparin

PROGESTIN-ONLY METHOD**Table 6. Progestin Only Contraceptive Methods**

Contraceptive	Mechanism of Action	Side Effects	Contraindications
<ul style="list-style-type: none"> Suitable for postpartum women (does not affect breast milk supply) Women with contraindications to combined OCP (e.g. thromboembolic or myocardial disease) Women intolerant of estrogenic side effects of combined OCPs 	<ul style="list-style-type: none"> Progestin prevents LH surge Thickening of cervical mucus Decrease tubal motility Endometrial decidualization Ovulation suppression – oral progestins (not IM) do not consistently suppress compared to combined OCPs 	<ul style="list-style-type: none"> Irregular menstrual bleeding Weight gain Headache Breast tenderness Mood changes Functional ovarian cysts Acne/oily skin Hirsutism 	<p>Absolute</p> <ul style="list-style-type: none"> None

**Missed Combined OCPs****Miss 1 pill**

- Take 1 pill as soon as patient remembers, and the next pill at the usual time; OR 2 pills at the next dose.

Miss 2 pills in a row during first 2 weeks of the cycle

- Take 2 pills the day patient remembers, and 2 pills the next day.
- Then 1 pill per day until pack is finished.
- Back-up method of birth control required during next 7 days.

Miss 2 pills in a row during third week of the cycle OR miss 3 in a row at any time

- Throw out pack and start a new pack immediately.
- Back-up method of birth control required during next 7 days.

**Missed Progestin-Only Pills**

Use back-up contraceptive method for at least 48 hours. Continue to take remainder of pills as prescribed.



Canadian Consensus Guideline on Continuous and Extended Hormonal Contraception (2007)

Definitions

*Extended use: The use of combined hormonal contraceptives with planned hormone-free intervals.

*Continuous Use: Uninterrupted use of combined hormonal contraceptive without hormone-free intervals.

What can be used?

Oral, transdermal and vaginally administered combined hormonal contraceptives, including those originally designed for cyclic use, can be administered in a variety of Continuous and Extended (C/E) regimens.

Efficacy and Adherence

Continuous combined hormonal contraceptive regimens are as effective as cyclic regimens in preventing pregnancy. Use of C/E combined hormonal contraceptive may be more "forgiving" about missed combined hormonal contraceptives because of the absence of a hormone-free interval.

Side Effects

The side effect profile of C/E combined hormonal contraceptive regimens is not worse than with cyclic regimens, and may be improved.

Medical/Non-contraceptive Usage

For women in the perimenopausal transition who may be ovulating, C/E combined hormonal contraceptive is preferred to hormonal replacement therapy for controlling problematic bleeding and vasomotor symptoms.

Journal of Obstetrics and Gynaecology Canada (2007) Vol 29, Suppl 2.



Types of IUDs

Copper containing: Nova-T®, Flexi-T®
Progesterone containing: Mirena®

Can be inserted for 5 years and fertility is restored with removal.

Consequences of Long-term Use of Depo-Provera®

Wooltorton E. CMAJ 2005; 172(6):746
Extended use (up to five years) of medroxyprogesterone acetate has been found to decrease spine and hip bone mineral density (BMD) by 4% to 6.9%. Two years after discontinuation, only partial recovery of BMD has been noted.

New SOGC Recommendations for Depo-Provera® Users

SOGC News Release. New recommendations from national ob/gyn society address Depo-Provera®, bone loss. May 2006. http://www.sogc.org/media/pdf/advisories/dmpa-may2006_e.pdf

- Inform patients of potential risks and benefits at intervals throughout course of treatment
- Recommend ways to improve bone health such as calcium, vitamin D, weight-bearing exercise, smoking cessation, decreased alcohol and reduced caffeine
- There is no evidence to suggest routine BMD testing

Selected Examples of Progestin-Only Methods

Progestin-Only Pill ("minipill")

- Micronor® 0.35 mg norethindrone
- taken daily at same time of day to ensure reliable effect; no pill free interval
- higher failure rate (1.1-13% with typical use, 0.51% with perfect use) than other hormonal methods
- ovulation inhibited in 60% of women; most have regular cycles (but may cause oligo/amenorrhea)
- highly effective if also post-partum breastfeeding

Depo-Provera®

- injectable depot medroxyprogesterone acetate
- dose 150 mg IM q12-14wks (convenient dosing)
- initiate within 5 days of beginning of normal menses, immediately postpartum in breastfeeding and non-breastfeeding women
- irregular spotting progresses to complete amenorrhea in 70% of women (after 1-2 years of use)
- highly effective 99%; failure rate 0.3%
- side effect: decreased bone density (may be reversible)
- disadvantage: restoration of fertility may take up to 1-2 years

Intrauterine Device (IUD)

Table 7. IUD Contraceptive Methods

Mechanism of Action	Side Effects	Contraindications
<ul style="list-style-type: none"> • Copper-containing IUD (Nova-T®): mild foreign body reaction in endometrium toxic to sperm and alters sperm motility • Progesterone-releasing IUD (Mirena®): decidualization of endometrium and thickening of cervical mucus; minimal effect on ovulation • Highly effective (95-99%); failure rate 0-1.2% • Contraceptive effects last 5 years • Reversible, private, convenient • May be used in women with contraindications to OCPs or wanting long-term contraception 	<ul style="list-style-type: none"> • Copper IUD: increased blood loss and duration of menses, dysmenorrhea • Progesterone IUD: bloating, headache • Breakthrough bleeding • Expulsion (5% in the first year, greatest in first month and in nulliparous women) • Uterine wall perforation (1/1000) on insertion • If pregnancy occurs with an IUD, increased risk of ectopic • Increased risk of PID (within first 10 days of insertion only) 	<p>Absolute</p> <ul style="list-style-type: none"> • Known or suspected pregnancy • Undiagnosed genital tract bleeding • Acute or chronic PID • Lifestyle risk for STIs* • Known allergy to copper (copper IUD only) • Wilson's disease (copper IUD only) <p>Relative</p> <ul style="list-style-type: none"> • Valvular heart disease • Past history of PID or ectopic pregnancy • Presence of prosthesis • Abnormalities of uterine cavity, intracavitary fibroids • Severe dysmenorrhea or menorrhagia (copper IUD only) • Cervical stenosis • Immunosuppressed individuals (e.g. HIV)

*Cervical swabs for gonorrhea and chlamydia should be done prior to IUD insertion

Emergency Postcoital Contraception (EPC)



Table 8. Emergency Contraceptive Methods

	Mechanism of Action	Side Effects	Contraindications
HORMONAL Yuzpe Method <ul style="list-style-type: none"> Used within 72 hours of unprotected intercourse; limited evidence of benefit up to 5 days Ovral® 2 tablets then repeat in 12 hours (ethinyl estradiol 100 µg/levonorgestrel 500 µg) Can substitute with any OCP as long as same dose of estrogen used 2% overall risk of pregnancy Efficacy decreased with time (e.g. less effective at 72 hours than 24 hours) "Plan B" <ul style="list-style-type: none"> Consists of levonorgestrel 750 µg q12h for 2 doses (can also take 2 doses together); taken within 72 hours of intercourse Greater efficacy (75-95% if used within 24 h) and better side effect profile than Yuzpe method but efficacy decreases with time No estrogen thus very few contraindications/side effects (less nausea) 	<ul style="list-style-type: none"> Unknown; suggestions include: <ul style="list-style-type: none"> Suppresses ovulation or causes deficient luteal phase Alters endometrium to prevent implantation Affects sperm/ova transport 	<ul style="list-style-type: none"> Nausea (due to estrogen; treat with Gravol®) Irregular spotting 	<ul style="list-style-type: none"> Pre-existing pregnancy (although not teratogenic) Caution in women with contraindications to OCP (although NO absolute contraindications)
NON-HORMONAL Postcoital IUD (Copper) <ul style="list-style-type: none"> Insert up to 7 days postcoitus Prevents implantation 1% failure rate Can use for short duration in higher risk individuals Mirena® IUD cannot be used as EPC 	<ul style="list-style-type: none"> See Table 7 	<ul style="list-style-type: none"> See Table 7 	<ul style="list-style-type: none"> See Table 7

Follow-up

- 3-4 weeks post treatment to confirm efficacy (confirmed by spontaneous menses or pregnancy test)
- contraception counseling



Any OCP can be used as EPC; 100 µg ethinyl estradiol PO q12h x 2 doses.

Infertility



Epidemiology

- 10-15% of couples
- must investigate both members of couple

Female Factors

Etiology

- ovulatory dysfunction (15-20%)**
 - hypothalamic (hypothalamic amenorrhea)
 - pituitary (prolactinoma, hypopituitarism)
 - ovarian
 - PCOS
 - premature ovarian failure
 - luteal phase defect (poor follicle production, premature corpus luteum failure, failed uterine lining response to progesterone), poorly understood
 - systemic diseases (thyroid, Cushing's syndrome, renal/hepatic failure)
 - congenital (Turner's syndrome, gonadal dysgenesis or gonadotropin deficiency)
 - stress, poor nutrition, excessive exercise (even with presence of menstruation)
- outflow tract abnormality**
 - tubal factors (20-30%)
 - PID
 - adhesions (previous surgery, peritonitis, endometriosis)
 - ligation/occlusion (e.g. previous ectopic pregnancy)
 - uterine factors (<5%)
 - congenital anomalies (e.g. prenatal DES exposure), bicornuate uterus, uterine septum
 - intrauterine adhesions (e.g. Asherman's syndrome)
 - infection (endometritis, pelvic TB)
 - fibroids/polyps (particularly intrauterine)
 - endometrial ablation
 - cervical factors (5%)
 - hostile or acidic cervical mucus
 - anti-sperm antibodies
 - structural defects (cone biopsies, laser or cryotherapy)



Infertility: inability to conceive or carry to term a pregnancy after one year of regular, unprotected intercourse.

Primary infertility: infertility in the context of no prior pregnancies.

Secondary infertility: infertility in the context of a prior conception.

Generally, 75% of couples achieve pregnancy within 6 months, 85% within 1 year, 90% within 2 years



Requirements for Conception

1. Ovary
2. Tube
3. Cervix
4. Endometrium
5. Sperm

**When should investigations begin?**

- <35 years: after 1 year of regular unprotected intercourse
- 35-40 years: after >6 months
- >40 years: immediately
- Earlier if:
 - History of PID
 - History of infertility in previous relationship
 - Prior pelvic surgery
 - Chemotherapy/radiation in either partner
 - Recurrent pregnancy loss
 - Moderate-severe endometriosis

**Controversial and Evolving Ethical Issues**

- Infertility demands non-judgmental discussion
- Ethical issues surrounding therapeutic donor insemination in same sex couples, surrogacy, donor egg and other advanced reproductive technologies are still evolving and remain controversial
- If certain options lie outside physician's moral boundaries, infertile couple should be referred to another physician

**Summary of Current Legislation in Canada****Bill C-13 Assisted Human Reproduction Act 2004:****WHAT IS NOT ALLOWED**

- Cloning people
- Cloning stem cells
- Growing human embryos for research
- Sex selection
- Making changes to human DNA that would pass from one generation to the rest
- Creating people who have animal DNA
- Buying or selling embryos, sperm, eggs or other human reproductive material

WHAT IS ALLOWED

- Surrogate mothers
- Donating sperm, eggs and other reproductive material
- Using embryos, sperm, eggs, etc., to assist conception
- Using human embryos and stem cells in research

**Normal Semen Analysis (WHO criteria)**

- Must be obtained after 48-72 hours of abstinence
 1. Volume 2-5 cc
 2. Count >20 million/cc
 3. Motility >50% forward progression
 4. Morphology >30% normal
 5. Absence of pyospermia, hyperviscosity, agglutination

NB: does not assess sperm function

- endometriosis (15-30%)
- multiple factors (30%)
- unknown factors (10-15%)

Investigations

- **ovulatory**
 - day 3: FSH, LH, TSH, PRL ± DHEA, free testosterone (if hirsute)
 - day 21-23: serum progesterone to confirm ovulation
 - initiate basal body temperature monitoring (biphasic pattern)
 - postcoital test: evaluate mucus for clarity, pH, spinnbarkeit (rarely done)
- **tubal factors**
 - HSG (can be therapeutic – opens fallopian tube)
 - SHG
 - laparoscopy with dye insufflation
- **peritoneal/uterine factors**
 - HSG/SHG, hysteroscopy
- **other**
 - karyotype

Treatment

- **education:** timing of intercourse in relation to ovulation (from 2 days prior to 2 days following presumed ovulation), every other day
- **medical**
 - ovulation induction
 - ♦ clomiphene citrate (Clomid®): estrogen antagonist that causes a perceived decreased estrogen state, resulting in increased pituitary gonadotropins; causes increased FSH and LH, leading to ovulation induction (better if anovulatory)
 - ♦ human menopausal gonadotropin [HMG (Pergonal®)], urofollitropin [FSH (Metrodin®)]
 - FSH and LH extracted from urine of postmenopausal women
 - ♦ followed by beta-hCG for stimulation of ovum release
 - may add
 - ♦ bromocriptine (dopamine agonist) if elevated prolactin
 - ♦ dexamethasone for hyperandrogenism (adult onset congenital adrenal hyperplasia), metformin (PCOS)
 - ♦ luteal phase progesterone supplementation for luteal phase defect
 - ♦ ASA (81 mg PO OD) daily for women with a history of recurrent spontaneous abortions
- **surgical/procedural**
 - tuboplasty
 - lysis of adhesions
 - artificial insemination
 - sperm washing
 - IVF (in vitro fertilization)
 - intrafallopian transfers
 - GIFT (gamete intrafallopian transfer): immediate transfer with sperm after oocyte retrieval
 - ZIFT (zygote intrafallopian transfer): transfer after 24 hour culture of oocyte and sperm
 - TET (tubal embryo transfer): transfer after >24 hour culture
 - ICSI (intracytoplasmic sperm injection)
 - IUI (intrauterine insemination)
 - ± oocyte or sperm donors
 - IVM (in vitro maturation)

Male Factors

- see Urology, U34

Etiology

- varicocele (>40%)
- idiopathic (>20%)
- obstruction (~15%)
- cryptorchidism (~8%)
- immunologic (~3%)

Investigations

- semen analysis and culture
- post-coital (Huhner) test: rarely done

Polycystic Ovarian Syndrome (PCOS)

- also called chronic ovarian androgenism

Etiology

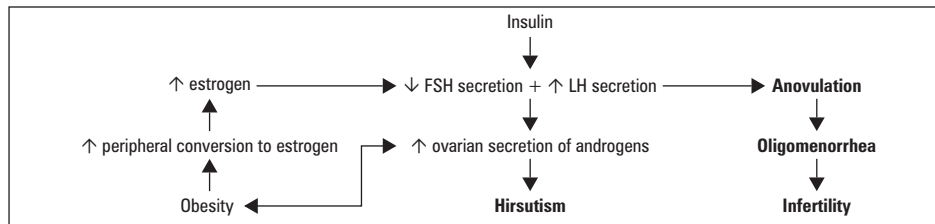


Figure 12. Pathophysiology of Polycystic Ovarian Syndrome

Diagnosis

- 2 of 3 to make diagnosis
 1. oligomenorrhea/irregular menses for 6 months
 2. clinical or lab evidence of hyperandrogenism
 3. polycystic ovaries on U/S

Clinical Features

- average age 15-35 years at presentation
- abnormal/irregular uterine bleeding, hirsutism, infertility, obesity, virilization
- insulin resistance occurs in both lean and obese patients
- acanthosis nigricans: browning of skin folds in intertriginous zones (indicative of insulin resistance)
- family history of diabetes

Investigations

- goal of investigations is to identify hyperandrogenism or chronic anovulation and rule out specific pituitary or adrenal disease as the cause
- labs
 - prolactin, 17-hydroxyprogesterone, free testosterone, DHEA-S, TSH, free T₄, androstenedione, sex hormone binding globulin (SHBG)
 - LH:FSH >2:1; LH is chronically high with FSH midrange or low (low sensitivity and specificity)
 - increased DHEAS, androstenedione and free testosterone (most sensitive), decreased SHBG
- transvaginal ultrasound: polycystic-appearing ovaries ("string of pearls")
- tests for insulin resistance or glucose tolerance
 - fasting glucose:insulin ratio <4.5 is consistent with insulin resistance (U.S. units)
 - 75g OGTT (particularly if obese)
- laparoscopy
 - not required for diagnosis
 - most common to see white, smooth, sclerotic ovary with a thick capsule; multiple follicular cysts in various stages of atresia; hyperplastic theca and stroma
- rule out other causes of abnormal bleeding

Treatment

- **cycle control**
 - lifestyle modification (decrease BMI, increase exercise) to decrease peripheral estrone formation
 - OCP monthly or cyclic Provera® to prevent endometrial hyperplasia due to unopposed estrogen
 - oral hypoglycemic (e.g. metformin)
 - tranexamic acid (Cyklokapron®) for menorrhagia only
- **infertility**
 - medical induction of ovulation: clomiphene citrate, human menopausal gonadotropins [hMG (Pergonal®)], LHRH, recombinant FSH, and metformin
 - ♦ metformin may be used alone or in conjunction with clomiphene citrate for ovulation induction
 - ovarian drilling (perforate the stroma), wedge resection of the ovary
 - bromocriptine (if hyperprolactinemia)
- **hirsutism**
 - any OCP can be used
 - ♦ Diane 35® (cyproterone acetate): antiandrogenic
 - ♦ Yasmin® (drospirenone and ethinyl estradiol): spironolactone analogue (inhibits steroid receptors)
 - mechanical removal of hair
 - finasteride (5-alpha reductase inhibitor)
 - flutamide (androgen reuptake inhibitor)



Clinical Signs of Endocrine Imbalance

- Menstrual disorder/amenorrhea (80%)
- Infertility (74%)
- Hirsutism (69%)
- Obesity (49%)
- Impaired glucose tolerance (35%)
- Diabetes Mellitus (10%)



Polycystic Ovarian Syndrome – HAIR-AN

Hirsutism, HyperAndrogenism, Infertility, Insulin Resistance, Acanthosis Nigricans



PCOS may be Confused with:

- Late onset congenital adrenal hyperplasia (21-hydroxylase deficiency)
- Cushing's syndrome
- Ovarian and adrenal neoplasms
- Hyperprolactinemia
- Hypothyroidism

Diagnostic Criteria for Polycystic Ovary Syndrome: Pitfalls and Controversies

Lujan ME et al. JGCM 2008.

At present, there is no clear-cut definition of biochemical hyperandrogenemia, particularly since there is dependence on poor laboratory standards for measuring androgens in women. Clinical signs of hyperandrogenism are ill-defined in women with PCOS, and diagnosis of both hirsutism and polycystic ovarian morphology remains subjective. There is also inappropriate tendency to assign ovulatory status solely on basis of menstrual cycle history or poorly timed endocrine measurements. Therefore it is important as clinicians to recognize the multi-factorial and complex nature of PCOS and place this in context of our present diagnostic limitations.



Long Term Health Consequences

- Hyperlipidemia
- Adult-onset diabetes mellitus
- Endometrial hyperplasia
- Infertility
- Obesity
- Sleep apnea

Use of Metformin in Polycystic Ovary Syndrome. A Meta-Analysis.

Obstet Gynecol 2008; 111(4):959-68.

Study: This meta-analysis of 17 RCTs assessed the efficacy of metformin or metformin in combination with clomiphene citrate in women with polycystic ovary syndrome (PCOS) who were seeking pregnancy.

Main Outcomes: Ovulation, pregnancy, and live birth.

Patients: 1,639 patients with PCOS were followed up for up to 12 months.

Results: Compared to placebo, metformin increased the odds of ovulation (OR 2.94, 95% CI 1.43 – 6.02). However, when used alone, metformin did not significantly increase the odds of achieving pregnancy (OR 1.56, 95% CI 0.74 – 3.33). When compared to clomiphene alone, the combination of metformin and clomiphene increased the likelihood of ovulation (OR 4.39, 95% CI 1.94 – 9.96) and pregnancy (OR 2.67, 95% CI 1.45 – 4.94). The effect of combination therapy was most prominent in clomiphene-resistant and obese women with PCOS. Furthermore, the combination therapy had a higher likelihood of having a live birth compared to clomiphene alone, but this did not reach significance (OR 1.74, 95% CI 0.79 – 3.86).

Conclusions: Metformin increases the likelihood of ovulation. When used together with clomiphene, metformin increases the likelihood of both ovulation and pregnancy, especially in clomiphene-resistant and obese women.



Gynecological Infections

Physiologic Discharge

- clear, white, flocculent odourless discharge; pH 3.8-4.2
- smear contains epithelial cells, *Lactobacilli*
- increases with increased estrogen states: pregnancy, OCP, mid-cycle, PCOS or premenarchal
- if increased in perimenopausal/postmenopausal woman, consider investigation for other effects of excess estrogen (e.g. endometrial cancer)

Vulvovaginitis

Vulvovaginitis

Vulvar and vaginal inflammation.



Most common gynecological problem in prepubertal girls is non-specific vulvovaginitis.



There is no high quality evidence showing a link between vulvovaginal candidiasis and hygienic habits or wearing tight or synthetic clothing.



Prepubertal and Adolescent Gynecological Infections: Legal Aspects of Confidentiality

- Clinicians who treat adolescents must be aware of federal, state and provincial laws related to adolescent consent and confidentiality.
- They must be aware of guidelines governing funding sources for particular services and be familiar with the consent and confidentiality policies of the facility in which they practice.

PREPUBERTAL VULVOVAGINITIS

• clinical features

- irritation, pruritus
- discharge
- vulvar erythema
- vaginal bleeding (specifically due to Group A *Streptococci* and *Shigella*)

• differential diagnosis

- non-specific vulvovaginitis (25-75%)
- infections (respiratory, enteric, systemic, sexually acquired)
- foreign body (toilet paper most common)
- candida (if using diapers)
- pinworms
- polyps, tumour (ovarian malignancy)
- vulvar skin disease (lichen sclerosis, condyloma acuminata)
- trauma (accidental straddle injury, sexual abuse)
- psychosomatic vaginal complaints (specific to vaginal discharge)
- endocrine abnormalities (specific to vaginal bleeding)
- blood dyscrasia (specific to vaginal bleeding)

• etiology

- infectious:
 - ♦ poor hygiene, proximity of vagina to anus
 - ♦ recent infection (respiratory, enteric, systemic)
 - ♦ STI: investigate sexual abuse
- nonspecific:
 - ♦ lack of protective hair and labial fat pads
 - ♦ lack of estrogenization
 - ♦ susceptible to chemicals, soaps (bubble baths), medications and clothing
 - ♦ enuresis

• investigations

- vaginal swab for culture (specifically state that it is a pre-pubertal specimen)

• treatment

- enhanced hygiene and local measures (handwashing, white cotton underwear, no nylon tights, no tight fitting clothes, no sleeper pajamas, sitz baths, avoid bubble baths, use mild detergent, eliminate fabric softener, avoid prolonged exposure to wet bathing suits, urination with legs spread apart)
- A&D® dermatological ointment to protect vulvar skin
- infectious: treat with antibiotics for organism identified

Table 9. Other Common Causes of Vulvovaginitis in Prepubertal Girls

	Pinworms	Lichen Sclerosis	Foreign Body
Diagnosis	Cellophane Tape test	Area of white patches and thinning of skin	
Treatment	Empirical treatment with mebendazole	Topical steroid creams	Irrigation of vagina with saline, may require local anesthesia or an exam under anesthesia

POSTMENOPAUSAL VAGINITIS/ATROPHIC VAGINITIS

- **clinical features**
 - dyspareunia
 - post-coital spotting
 - mild pruritus
- **investigations**
 - atrophy is usually a visual diagnosis: thinning of tissues, erythema, petechiae, bleeding points, dryness on speculum exam
 - rule out malignancy: especially endometrial cancer
- **treatment**
 - local estrogen replacement (ideal): Premarin® cream, VagiFem® tablets, or Estrin®
 - oral or transdermal hormone replacement therapy (if treatment for systemic symptoms is desired)
 - good hygiene

INFECTIOUS VULVOVAGINITIS**Table 10. Infectious Vulvovaginitis**

	Candidiasis (Moniliasis)	Bacterial Vaginosis (BV)	Trichomoniasis
Organisms	<i>Candida albicans</i> (90%) <i>Candida glabrata</i> (<5%) <i>Candida tropicalis</i> (<5%)	<i>Gardnerella vaginalis</i> <i>Mycoplasma hominis</i> Anaerobes: <i>Prevotella</i> , <i>Mobiluncus</i> , <i>Bacteroides</i>	<i>Trichomonas vaginalis</i> (flagellated protozoan)
Pathophysiology or Transmission	Predisposing factors include: <ul style="list-style-type: none"> • Immunosuppressed host (diabetes, AIDS, etc.) • Recent antibiotic use • Includes estrogen levels (e.g. pregnancy, OCP) 	Replacement of vaginal <i>Lactobacillus</i> with organisms above	Sexually transmitted
Discharge	Whitish, "cottage cheese," minimal	Grey, thin, diffuse	Yellow-green, malodorous, diffuse
Other	• 20% asymptomatic	• 50-75% asymptomatic	• 25% asymptomatic
Signs/Symptoms	• Intense pruritus • Swollen, inflamed genitals • Vulvar burning, dysuria, dyspareunia	• Fishy odour, esp. after coitus • Absence of vulva/vaginal irritation	• Petechiae on vagina and cervix • Occasionally irritated tender vulva • Dysuria, frequency
pH	≤4.5	>4.5	≤4.5
Saline Wetmount	KOH wetmount reveals hyphae and spores	1) >20% clue cells = squamous epithelial cells dotted with coccobacilli (<i>Gardnerella</i>) 2) Paucity of WBC 3) Paucity of <i>Lactobacilli</i> 4) Positive whiff test = fishy odour with addition of KOH to slide (due to formation of amines)	1) Motile flagellated organisms 2) Many WBC 3) Inflammatory cells (PMNs)
Treatment	<ul style="list-style-type: none"> • Clotrimazole, butoconazole, miconazole, terconazole suppositories and/or creams for 1, 3 or 7-day treatments • Treatment in pregnancy is usually topical treatment • fluconazole 150 mg PO in single dose 	<ul style="list-style-type: none"> • No treatment if non-pregnant and asymptomatic, unless scheduled for pelvic surgery or procedure Oral <ul style="list-style-type: none"> • Metronidazole 500 mg PO bid x 7 days or metronidazole gel 0.75% x 5 day OD • Clindamycin 2% 5 g intravaginally at bedtime for 7 days Topical <ul style="list-style-type: none"> • May use metronidazole in pregnancy 	<ul style="list-style-type: none"> • Treat even if asymptomatic! • Metronidazole 2 g PO single dose or 500 mg bid x 7 days (alternative) • Symptomatic pregnant women should be treated with 2 g metronidazole once
Other	<ul style="list-style-type: none"> • For repeat infections prophylaxis, treatment includes boric acid, vaginal suppositories, luteal phase fluconazole • Routine treatment of partner(s) not recommended (not sexually transmitted) 	<ul style="list-style-type: none"> • Associated with recurrent and preterm labour, preterm birth and postpartum endometritis in pregnancy • Need to warn patients on metronidazole not to consume alcohol (disulfiram-like action) • Routine treatment of partner(s) not recommended (not sexually transmitted) 	<ul style="list-style-type: none"> • Warnings accompanying metronidazole use • Treat partner(s)



Sexually Transmitted Infections (STIs)

- see Family Medicine, FM43



STI Testing

1. Vaginal swab
 - Tests for bacterial vaginosis, trichomoniasis, candida
2. Cervical swab
 - Test for gonorrhea and chlamydia



Risk Factors for STIs

- History of previous STI
- Contact with infected person
- Sexually active individual age <25 years
- Multiple partners
- New partner in last 3 months
- Not using barrier protection
- Street involvement (homelessness, drug use)



Public Health Agency of Canada: National Notifiable STIs

- HIV
- Gonorrhea
- Chlamydia
- Syphilis
- Hepatitis B, C, D

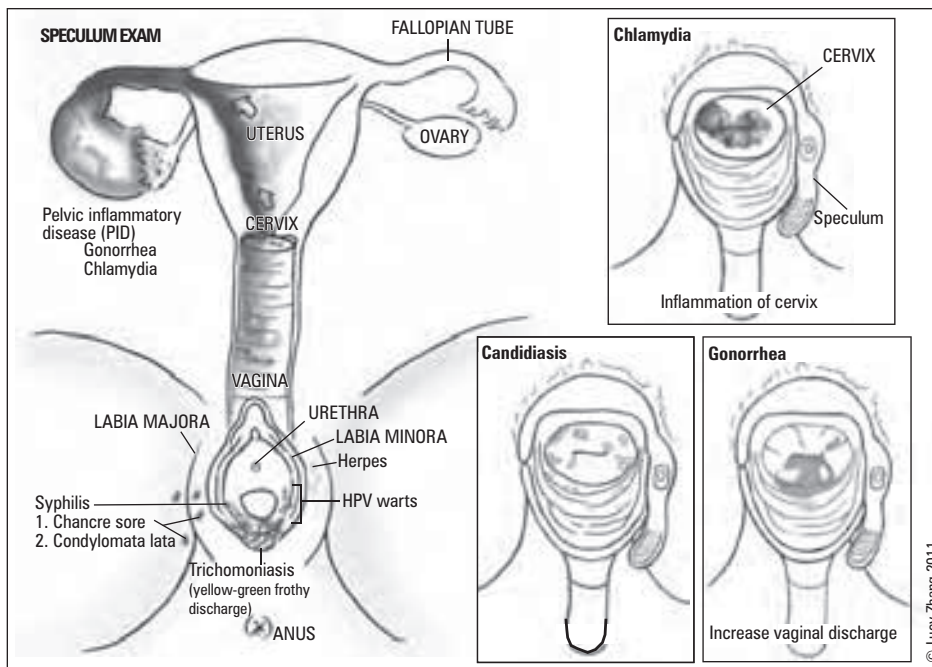


Figure 13. Speculum Exam

TRICHOMONIASIS

- see *Infectious Vulvovaginitis*, GY25

CHLAMYDIA

Etiology

- *Chlamydia trachomatis*

Epidemiology

- most common bacterial STI in Canada
- often associated with *N. gonorrhoeae*

Clinical Features

- asymptomatic (80% of women)
- muco-purulent endocervical discharge
- urethral syndrome: dysuria, frequency, pyuria, no bacteria
- pelvic pain
- post-coital bleeding or intermenstrual bleeding (particularly if on OCP and prior history of good cycle control)
- symptomatic sexual partner

Investigations

- cervical culture or nucleic acid amplification test
- obligate intracellular parasite – tissue culture is the definitive standard
- urine and vaginal test now available, which are equally or more effective than cervical culture

Treatment

- doxycycline 100 mg PO bid for 7d or azithromycin 1 g PO in a single dose (may use in pregnancy)
- also treat gonorrhea because of high rate of co-infection
- treat partners
- reportable disease
- test of cure for chlamydia required in pregnancy (cure rates lower in pregnant patients) → re-test 3-4 weeks after initiation of therapy

Screening

- high risk groups
- during pregnancy

Complications

- acute salpingitis, PID
- Fitz-Hugh-Curtis syndrome (liver capsule infection)
- arthritis, conjunctivitis, urethritis (reactive arthritis – male predominance, HLA-B27)
- infertility – tubal obstruction from low grade salpingitis
- ectopic pregnancy
- chronic pelvic pain
- perinatal infection – conjunctivitis, pneumonia

GONORRHEA**Etiology**

- *Neisseria gonorrhoeae*
- symptoms and risk factors same as with chlamydia

Investigations

- Gram stain shows Gram-negative intracellular diplococci
- cervical, rectal and throat culture

Treatment

- single dose of ceftriaxone 125 mg IM, or cefixime 400 mg PO, or ciprofloxacin 500 mg PO
- if pregnant – cephalosporin regimen or 2 g spectinomycin IM (avoid quinolones)
- also treat chlamydia, because of high rate of co-infection
- treat partners
- reportable disease
- screening as with chlamydia

HUMAN PAPILLOMAVIRUS (HPV)**Etiology**

- most common viral STI in Canada
- >200 subtypes, of which >30 are genital subtypes
- HPV types 6 and 11 are classically associated with anogenital warts/condylomata acuminata
- HPV types 16 and 18 are the most oncogenic (classically associated with cervical HSIL)
- types 16, 18, 31, 33, 35, 36, 45 (and others) associated with increased incidence of cervical and vulvar intraepithelial hyperplasia and carcinoma

Clinical Features

- latent infection
 - no visible lesions, asymptomatic
 - only detected by DNA hybridization tests
- subclinical infection
 - visible lesion found during colposcopy or on Pap test
- clinical infection
 - visible wart-like lesion without magnification
 - hyperkeratotic, verrucous or flat, macular lesions
 - vulvar edema

Investigations

- cytology (see *Cervical Screening (Pap Test)*, GY43)
 - koilocytosis – nuclear enlargement and atypia with perinuclear halo
- biopsy of lesions at colposcopy
- detection of HPV DNA subtype using nucleic acid probes not routinely done but can be done in presence of abnormal Pap test to guide treatment

Treatment

- patient administered:
 - podofilox 0.5% solution or gel bid x 3 days in a row (4 days off) then repeat x 4 weeks
 - imiquimod (Aldara®) 5% cream 3x/wk qhs x 16wks
- provider administered:
 - cryotherapy with liquid nitrogen: repeat q1-2wks
 - podophyllin resin in tincture of benzoin: weekly
 - trichloroacetic acid (TCA) or bichloroacetic acid weekly (80-90%); safe in pregnancy
 - surgical removal/laser
 - intralesional interferon

Prevention

- HPV types 6, 11, 16, 18 – preventable with Gardasil® (quadrivalent HPV recombinant vaccine)
- cannot be prevented by using condoms



Test of cure for *C. trachomatis* and *N. gonorrhoeae* is not routinely indicated. Repeat testing if symptomatic, if compliance with treatment is uncertain, or if pregnant.

**Genital Warts During Pregnancy**

- Condyloma tend to get larger in pregnancy and should be treated early (consider excision).
- C-section only if obstruction of birth canal or risk of extensive bleeding.
- Do not use imiquimod, podophyllin or podofilox.

**Human Rights in Health Equity: Cervical Cancer and HPV Vaccines**

Erdman, JN. *American Journal of Law & Medicine*. 2009

- While cervical cancer rates have drastically fallen in developed countries due to effective prevention and treatment, socially disadvantaged women within these countries remain disproportionately more likely to develop and die of cervical cancer.
- In most developing countries, in contrast, cervical cancer rates have risen or remained unchanged.
- Must recognize that cervical cancer disparities between race groups, urban and rural residence, and high and low wealth status are attributed to disparate screening and vaccination coverage.
- Programs are implemented without sufficient attention to conditions that render screening less effective or inaccessible to disadvantaged social groups including: lack of information, undervaluing of preventive care, opportunistic delivery in limited health care settings, sexual health stigma and related privacy concerns.

HERPES SIMPLEX VIRUS OF VULVA (HSV)

Etiology

- 90% are HSV-2, 10% are HSV-1

Clinical Features

- may be asymptomatic
- initial symptoms: present 2-21 days following contact
- prodromal symptoms: tingling, burning, pruritus
- multiple, painful, shallow ulcerations with small vesicles appear 7-10 days after initial infection (absent in many infected persons); lesions are infectious
- inguinal lymphadenopathy, malaise, and fever often with first infection
- dysuria and urinary retention if urethral mucosa affected
- recurrent infections: less severe, less frequent and shorter in duration (especially with HSV-1)

Investigations

- viral culture preferred in patients with ulcer present – decreased sensitivity as lesions heal
- cytologic smear
 - multinucleated giant cells, acidophilic intranuclear inclusion bodies
- type specific serologic tests for antibodies to HSV-1 and HSV-2 (not available routinely in Canada)
- HSV DNA PCR

Treatment

- first episode
 - acyclovir 400 mg PO tid x 7-10d, or famciclovir 250 mg PO tid x 7-10d, or valacyclovir 1 g PO bid x 7-10d
- recurrent episode
 - acyclovir 400 mg PO tid x 3-5d, or famciclovir 125 mg PO bid x 3-5d, or valacyclovir 500 mg PO bid x 3d
- daily suppressive therapy
 - consider if 6-8 recurrences per year
 - acyclovir 400 mg PO bid, or famciclovir 250 mg bid, or valacyclovir 0.5-1 g PO OD
- severe disease
 - consider IV therapy acyclovir 5-10 mg/kg IV q8h x 5-7d
- education regarding transmission
- avoid contact from onset of prodrome until lesions have cleared
- use barrier contraception

SYPHILIS

Etiology

- *Treponema pallidum*

Classifications

- progresses in stages
- **primary syphilis**
 - 3-4 weeks after exposure
 - painless chancre on vulva, vagina or cervix
 - painless inguinal lymphadenopathy
 - serological tests usually negative, local infection only
- **secondary syphilis** (can resolve spontaneously)
 - 2-6 months after initial infection
 - nonspecific symptoms: malaise, anorexia, headache, diffuse lymphadenopathy
 - generalized maculopapular rash: palms, soles, trunk, limbs
 - condylomata lata: anogenital, broad-based fleshy grey lesions
 - serological tests usually positive
- **latent syphilis**
 - no clinical manifestations; detected by serology only
- **tertiary syphilis**
 - may involve any organ system
 - neurological: tabes dorsalis, general paresis
 - cardiovascular – aortic aneurysm, dilated aortic root
 - vulvar gumma: nodules that enlarge, ulcerate and become necrotic (rare)
- **congenital syphilis**
 - may cause fetal anomalies, stillbirths or neonatal death



Classically...

HSV I – disease above the belt (oral)

HSV II – disease below the belt (genital)



HSV Infections During Pregnancy

- Antiviral suppression of women with first episode or history of HSV infections from 36 weeks GA on.
- C-section should be performed on women who have active genital lesions at time of delivery.
- Treatment: acyclovir 400 mg PO tid.



Epidemiology of Genital Ulcers

HSV	70-80%
1° syphilis	5%
Chancroid	<1%

Investigations

- aspirate of ulcer serum or node
- darkfield microscopy (most sensitive and specific diagnostic test for syphilis)
 - spirochetes
- non-treponemal screening tests (VDRL, RPR); nonreactive after treatment, can be positive with other conditions
- specific anti-treponemal antibody tests (FTA-ABS, MHA-TP, TP-PA)
 - confirmatory tests; remain reactive for life (even after adequate treatment)

Treatment

- treatment of primary, secondary, latent syphilis of <1 year duration
 - benzathine penicillin G 2.4 million units IM single dose
 - treat partners, reportable disease
- treatment of latent syphilis >1 year duration
 - benzathine penicillin G 2.4 million units IM q1wk x 3 weeks
- treatment of neurosyphilis
 - IV aqueous penicillin G 3-4 million units IM q4h for 10-14 days
- screening
 - high risk groups
 - in pregnancy (see Obstetrics, Table 10, OB19)

Complications

- if untreated, 1/3 will experience late complications

HIV

- see Infectious Diseases, ID29

Bartholinitis/Bartholin Gland Abscess

Etiology

- often anaerobic and polymicrobial
- *U. urealyticum*, *N. gonorrhoeae*, *C. trachomatis*, *E. coli*, *P. mirabilis*, *Streptococcus* spp., *S. aureus* (rare)
- blockage of duct

Clinical Features

- unilateral swelling and pain in inferior lateral opening of vagina
- sitting and walking may become difficult and/or painful

Treatment

- sitz baths, warm compresses
- antibiotics
- incision and drainage using local anesthesia with placement of Word catheter (10 Fr. latex catheter) for 2-3 weeks
- marsupialization under general anesthetic – more definitive treatment
- rarely treated by removing gland

Pelvic Inflammatory Disease (PID)

- up to 20% of all gynecology-related hospital admissions

Etiology

- causative organisms (in order of frequency)
 - *C. trachomatis*
 - *N. gonorrhoeae*
 - gonorrhea and chlamydia often co-exist
 - endogenous flora: anaerobic, aerobic, or both
 - ♦ *E. coli*, *Staphylococcus*, *Streptococcus*, *Bacteroides*, *Peptostreptococcus*, *H. influenzae*, *G. vaginalis*
 - ♦ cause of recurrent PID
 - ♦ associated with instrumentation
 - *Actinomyces israelii* (Gram-positive, non acid-fast anaerobe)
 - ♦ in 1-4% of PID associated with IUDs
 - others (TB, Gram-negatives, CMV, *U. urealyticum*, etc.)

Risk Factors

- age <30 years
- risk factors as for chlamydia and gonorrhea
- vaginal douching
- IUD (within first 10 days after insertion)
- invasive gynecologic procedures (D&C, endometrial biopsy)

PID

Inflammation of the upper genital tract (above cervix) including endometrium, fallopian tubes, ovaries, pelvic peritoneum, ± contiguous structures.



PID accounts for up to 20% of all gynecology hospital admissions.

**PID Diagnosis**

- **Must** have:
 - Lower abdominal pain
 - Cervical motion tenderness
 - Adnexal tenderness
- **Plus** one or more of:
 - High risk partner
 - Temperature >38°C
 - Mucopurulent cervical discharge
 - Positive culture for *N. gonorrhoeae*, *C. trachomatis*, *E. coli*, or other vaginal flora
 - Cul-de-sac fluid, pelvic abscess or inflammatory mass on U/S or bimanual
 - Leukocytosis
 - Elevated ESR or CRP (not commonly used)

Clinical Presentation

- up to 2/3 asymptomatic: many subtle or mild symptoms
- common
 - fever >38.3°C
 - lower abdominal pain and tenderness
 - abnormal discharge: cervical or vaginal
- uncommon
 - nausea and vomiting
 - dysuria
 - AUB
- chronic disease (often due to chlamydia)
 - constant pelvic pain
 - dyspareunia
 - palpable mass
 - very difficult to treat, may require surgery

Investigations

- bloodwork
 - β -hCG (must rule out ectopic pregnancy), CBC, blood cultures if suspect septicemia
- urine R&M
- speculum exam, bimanual exam
 - vaginal swab for Gram stain, C&S
 - cervical cultures for *N. gonorrhoeae*, *C. trachomatis*
 - endometrial biopsy will give definitive diagnosis (rarely done)
- ultrasound
 - may be normal
 - free fluid in cul-de-sac
 - pelvic or tubo-ovarian abscess
 - hydrosalpinx (dilated fallopian tube)
- laparoscopy (gold standard)
 - for definitive diagnosis: may miss subtle inflammation of tubes or endometritis

Treatment

- must treat with polymicrobial coverage
- **inpatient if:**
 - moderate to severe illness
 - atypical infection
 - adnexal mass, tubo-ovarian or pelvic abscess
 - unable to tolerate oral antibiotics or failed oral therapy
 - immunocompromised
 - pregnant
 - adolescent – first episode
 - surgical emergency cannot be excluded (e.g. ovarian torsion)
 - PID is secondary to instrumentation
 - recommended treatment
 - ♦ cefoxitin 2 g IV q6h (no longer available in U.S.A.) or cefotetan 2 g IV q12h + doxycycline 100 mg IV/PO q12h or
 - ♦ clindamycin 900 mg IV q8h + gentamicin 2 mg/kg IV loading dose then gentamicin 1.5 mg/kg q8h maintenance dose
 - ♦ continue IV antibiotics for 24 hours after symptoms have improved then doxycycline 100 mg PO bid to complete 14 days
 - ♦ percutaneous drainage of abscess under U/S guidance
 - ♦ when no response to treatment, laparoscopic drainage
 - ♦ if failure, treatment is surgical (salpingectomy, TAH/BSO)
- **outpatient if:**
 - typical findings
 - mild to moderate illness
 - oral antibiotics tolerated
 - compliance ensured
 - follow-up within 48-72 hours (to ensure symptoms not worsening)
 - recommended treatment
 - ♦ ofloxacin 400 mg PO bid x 14d or levofloxacin 500 mg PO bid x 14d ± metronidazole 500 mg PO bid x 14d (if suspect abscess)
 - ♦ ceftriaxone 250 mg IM x 1 + doxycycline 100 mg PO bid x 14d or cefoxitin 2 g IM x 1 + probenecid 1 g PO + doxycycline 100 mg PO bid ± metronidazole 500 mg PO bid x 14d
 - ♦ consider removing IUD after a minimum of 24 hours of treatment
 - ♦ reportable disease
 - ♦ treat partners
 - ♦ consider re-testing for *C. trachomatis* and *N. gonorrhoeae* 4-6 weeks after treatment if documented infection



Treat PID with
FOXY DOXY
(cefoxitin + doxycycline)



For patients with contraindications to treatment with cephalosporins or quinolones, recent evidence suggests that a short course of azithromycin at a dose of either 250 mg PO daily for one week or 1 g PO weekly for two weeks combined with metronidazole is effective in achieving a clinical cure for acute PID.

Source: Update to the Canadian Guidelines on Sexually Transmitted Infections. October 2008.

Complications of Untreated PID

- chronic pelvic pain
- abscess, peritonitis
- adhesion formation
- ectopic pregnancy
- infertility
 - 1 episode of PID → 13% infertility
 - 2 episodes of PID → 36% infertility
- bacteremia
- septic arthritis, endocarditis

**PID Complications****I FACE PID**

Infertility
 Fitz-Hugh-Curtis syndrome
 Abscesses
 Chronic pelvic pain
 Ectopic pregnancy
 Peritonitis
 Intestinal obstruction
 Disseminated infection (sepsis, endocarditis, arthritis, meningitis)

Toxic Shock Syndrome

- see Infectious Diseases, ID27

Risk Factors

- tampon use
- diaphragm, cervical cap or sponge use (prolonged use, i.e. >24 hours)
- wound infections
- post-partum infections
- early recognition and treatment of syndrome is imperative as incorrect diagnosis can be fatal

Clinical Presentation

- sudden high fever
- sore throat, headache, diarrhea
- erythroderma
- signs of multisystem organ failure
- refractory hypotension
- exfoliation of palmar and plantar surfaces of the hands and feet 1-2 weeks after onset of illness

Treatment

- remove potential sources of infection (foreign objects and wound debris)
- debride necrotic tissues
- adequate hydration
- penicillinase-resistant antibiotics, e.g. cloxacillin
- steroid use controversial but if started within 72 hours, may reduce severity of symptoms and duration of fever

Toxic Shock Syndrome

Multiple organ system failure due to *S. aureus* exotoxin (rare condition).

Surgical Infections

Post-Operative Infections in Gynecological Surgery

- pelvic cellulitis
 - common post hysterectomy, affects vaginal vault
 - erythema, induration, tenderness, discharge involving vaginal cuff
 - treat if fever and leukocytosis with broad spectrum antibiotics, i.e. clindamycin and gentamicin
 - drain if excessive purulence or large mass
 - can result in intra-abdominal and pelvic abscess
- see General Surgery, *Post-Operative Fever*, GS7

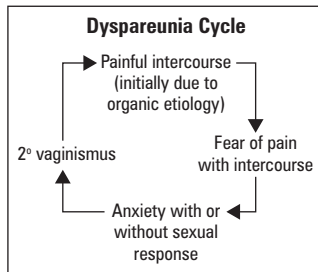
Sexuality and Sexual Dysfunction

SEXUAL RESPONSE

1. desire: energy that allows an individual to initiate or respond to sexual stimulation
2. arousal: physical and emotional stimulation leading to breast and genital vasodilation and clitoral engorgement
3. orgasm: physical and emotional stimulation is maximized, allowing the individual to relinquish their sense of control
4. resolution: most of the congestion and tension resolves within seconds, complete resolution may take up to 60 minutes

SEXUAL DYSFUNCTION**Etiology**

- intrapsychic: patient's life experiences, value system
- relationship/interpersonal issues
- physical/organic



Classification

- lack of desire (60-70% of women)
- lack of arousal
- anorgasmia (5-10%)
 - primary anorgasmia: never before achieved orgasm under any circumstances
 - secondary anorgasmia: was able to achieve orgasms before but now unable
- dyspareunia (3-6%) – painful intercourse, superficial or deep
 - vaginismus (15%)
 - vulvodynia
 - vaginal atrophy
 - vulvar vestibulitis: associated with history of frequent yeast infections
 - PID

Treatment

- lack of desire – assess factors, rule out organic causes, relationship therapy, sensate focus exercises
- anorgasmia – self-exploration/pleasuring, relationship therapy if needed, bridging techniques (different sexual positions, clitoral stimulation during intercourse)
- dyspareunia
 - Kegel and reverse Kegel exercises
 - dilator treatment
 - comfort with self-exam
 - psychotherapy, other behavioural techniques
 - female on top position – allows for control of speed and duration
 - vestibulitis – remove local irritants, change in contraceptive methods, and dietary changes (increased citrate, decreased oxalate), vestibulectomy (rare)
 - vulvodynia – local moisturization, cold compresses, systemic nerve blocking therapy (amitriptyline, neurontin), topical anesthetic, estrogen cream



Kegel Exercises

Regular contraction and relaxation to strengthen pelvic floor muscles.

Reverse Kegel Exercises

1 second contraction then 5 seconds of relaxation.



Menopause

- see Family Medicine, FM41

Definitions

- types of menopause
 - physiological; average age 51 years (follicular atresia)
 - premature ovarian failure; before age 40 (autoimmune disorder, infection, Turner's syndrome)
 - iatrogenic (surgical/radiation/chemotherapy)

Clinical Features

- associated with estrogen deficiency
 - vasomotor instability (tends to dissipate with time)
 - ♦ hot flushes/flushes, night sweats, sleep disturbances, formication, nausea, palpitations
 - urogenital atrophy involving vagina, urethra, bladder
 - ♦ dyspareunia, vaginal itching, vaginal dryness, bleeding, urinary frequency, urgency, incontinence
 - skeletal
 - ♦ osteoporosis, joint and muscle pain, back pain
 - skin and soft tissue
 - ♦ decreased breast size, skin thinning/loss of elasticity
 - psychological
 - ♦ mood disturbance, irritability, fatigue, decreased libido, memory loss

Investigations

- increased levels of FSH (>35 IU/L) on day 3 of cycle (if still cycling) and LH (FSH>LH)
- decreased levels of estradiol (later)

Treatment

- goal is for individual symptom management
 - vasomotor instability
 - ♦ HRT (first line), clonidine, SSRI, Effexor®, gabapentin, propranolol
 - vaginal atrophy
 - ♦ local estrogen – cream (Premarin®), vaginal suppository (VagiFem®), ring (Estring®)
 - ♦ lubricants (Replens®)
 - urogenital health
 - ♦ lifestyle changes (weight loss, bladder re-training), local estrogen replacement, surgery



- **Menopause:** occurrence of last spontaneous menstrual period, resulting from loss of ovarian function (loss of oocyte response to gonadotropins).

- **"Being in menopause":** lack of menses for 1 yr.

- **Perimenopause:** period of time surrounding menopause (2-8 yrs preceding + 1 yr after last menses) characterized by fluctuating hormone levels, irregular menstrual cycles, and symptom onset.



- 85% of women experience hot flashes
- 20-30% seek medical attention
- 10% are unable to work



- Osteoporosis is the single most important health hazard associated with menopause.
- Cardiovascular disease is the leading cause of death post-menopause.



- Increased risk of breast cancer (RR 1.3) is associated with HRT use.
- All women taking HRT should have periodic surveillance and counselling regarding its benefits and risks.

- osteoporosis
 - 1000-1500 mg calcium daily, 800-1000 IU vitamin D, weight-bearing exercise, quit smoking
 - bisphosphonates (e.g. alendronate)
 - selective estrogen receptor modifiers (SERMs): raloxifene (Evista®) – mimics estrogen effects on bone, avoids estrogen-like action on breast and uterine cancer; does not help hot flashes
 - HRT: second-line treatment (unless for vasomotor instability as well)
- decreased libido
 - vaginal lubrication, counselling, androgen replacement (testosterone cream)
- cardiovascular disease
 - management of cardiovascular risk factors
- mood and memory
 - antidepressants (first line), HRT (augments effect)
- alternative choices (not evidence-based, safety not established)
 - black cohosh, phytoestrogens, St. John's wort, ginkgo biloba, valerian, evening primrose oil, ginseng, Don Quai

Hormone Replacement Therapy (HRT)

- see [Family Medicine](#), FM41
- primary indication is treatment of menopausal symptoms (vasomotor instability)
- keep doses low (e.g. 0.3 mg Premarin®) and duration of treatment short (<5 years)

HRT Components

- estrogen
 - oral or transdermal (e.g. patch, gel)
 - transdermal preferred for women with hypertriglyceridemia or impaired hepatic function
 - low-dose (e.g. 0.3 mg Premarin®/25 µg Estradot® patch)
- progestin
 - given in combination with estrogen for women with an intact uterus to prevent development of endometrial hyperplasia/cancer

Table 11. Examples of HRT Regimens

HRT Regimen	Estrogen Dose	Progestin Dose	Notes
Unopposed Estrogen	CEE 0.625 mg PO OD	None	If no intact uterus
Standard-dose	CEE 0.625 mg PO OD	MPA 2.5 mg PO OD	Withdrawal bleeding may occur in a spotty, unpredictable manner Usually abates after 6-8 months due to endometrial atrophy Once patient has become amenorrheic on HRT, significant subsequent bleeding episodes require evaluation (endometrial biopsy)
Standard-dose Cyclic	CEE 0.625 mg PO OD	MPA 5-10 mg PO days 1-14 only	Bleeding occurs monthly after day 14 of progestin (can continue for years) PMS-like symptoms (breast tenderness, fluid retention, headache, nausea) are more prominent with cyclic HRT
Pulsatile	CEE 0.625 mg PO OD	MPA low-dose	3 days on, 3 days off
Transdermal	Estroderm®-Estradiol 0.05 mg/d or 0.1 mg/d Estalis®-Estradiol® 140 µg/d or 250 µg/d	Estroderm®-MPA 2.5 mg PO OD Estalis®-NEA 50 µg/d	Use patch twice weekly Can use oral progestins (Estroderm®) Combined patches available (Estalis®)

CEE = conjugated equine estrogen (e.g. Premarin®); MPA = medroxyprogesterone acetate (e.g. Provera®); NEA = norethindrone acetate
Consider lower dose regimens, PREMPRO® 0.45/1.5 (Premarin 0.45 mg and Provera 1.5 mg)

Side Effects of HRT

- abnormal uterine bleeding
- mastodynia – breast tenderness
- edema, bloating, heartburn, nausea
- mood changes (progesterone)
- can be worse in progesterone phase of combined therapy

Contraindications to HRT

- absolute
 - acute liver disease
 - undiagnosed vaginal bleeding
 - known or suspected uterine cancer/breast cancer
 - acute vascular thrombosis or history of severe thrombophlebitis or thromboembolic disease



Menopause Pathophysiology

Degenerating theca cells fail to react to endogenous gonadotropins (FSH, LH)

↓
Less estrogen is produced

↓
Decreased negative feedback on hypothalamic-pituitary-adrenal axis

↓
Increased FSH and LH

↓
Stromal cells continue to produce androgens as a result of increased LH stimulation



Absolute Contraindications to HRT

ABCD

Acute liver disease
Breast cancer (undiagnosed)
Cancer (breast/uterine)
DVT (thromboembolic disease)

Excerpt from the SOGC 2006 Menopause Consensus Report

The primary indication for HRT is for the management of moderate to severe menopausal symptoms. HRT should be prescribed at the lowest effective dose for the appropriate duration to achieve treatment goals.

- relative
 - pre-existing uncontrolled hypertension
 - uterine fibroids and endometriosis
 - familial hyperlipidemias
 - migraine headaches
 - family history of estrogen-dependent cancer
 - chronic thrombophlebitis
 - diabetes mellitus (with vascular disease)
 - gallbladder disease, hypertriglyceridemia, impaired liver function (consider transdermal estrogen)
 - fibrocystic disease of the breasts

WOMEN'S HEALTH INITIATIVE (WHI) (launched in 1991)

- two non-randomized studies investigating health risks and benefits of hormone therapy in healthy postmenopausal women 50-79 years old; the WHI Extension Study, involving follow-up health tracking without intervention, is due to last through 2010
 - continuous combined HRT (CEE 0.625 mg + MPA 2.5 mg OD) in 16,608 women with an intact uterus
 - ♦ originally designed to run 8.5 years – stopped early after 5.2 years (July 2002) because the evidence for harm (breast cancer, CHD, stroke, PE) outweighed benefit (fracture reduction, colon cancer reduction)
 - estrogen-alone (CEE 0.625 mg) in 10,739 women with a previous hysterectomy also stopped early (February 2004 instead of March 2005) because of increased stroke risk and no heart disease benefit
- benefits and risks reported as number of cases per 10,000 women each year

HRT Benefits

- protective against osteoporotic fractures (recommended as 2nd line treatment only)
 - hip fractures – 5 fewer cases with combined HRT (6 fewer cases with estrogen-alone)
 - all fractures – 47 fewer cases with combined HRT
- colon cancer – 6 fewer cases with combined HRT (1 additional case with estrogen-alone)

HRT Risks

- invasive breast cancer – 8 additional cases with combined HRT
 - risk comparable to being 20% overweight, lacking regular exercise, fewer pregnancies after 30 years of age, reduced breastfeeding, excessive alcohol or cigarette use
 - NO increased risk with estrogen-alone (7 **fewer** cases)
- coronary heart disease – 7 additional MIs with combined HRT
 - no significant difference in cardiac deaths between treatment and control groups
 - NO elevated heart risks if used immediately after menopause (~45-55 years of age), or with estrogen-alone (5 **fewer** cases)
- DVTs or PEs – 18 additional cases with combined HRT
 - 9 additional cases for women taking estrogen-alone
- stroke – 8 additional cases with combined HRT (not statistically significant)
 - 12 additional cases with estrogen-alone
- dementia and mild cognitive impairment (WHI Memory Score)
 - women taking estrogen-alone before 65 years of age were less likely to develop dementia, **however** there was a 50% **increased** risk of developing dementia when taken after 65 years of age (those taking combined HRT were at even greater risk)
 - “window of opportunity” hypothesis: early use of estrogen (before pre-dementia changes) protects the healthy brain; in older women, where changes have already begun, use of estrogen accelerates the dementia process
- there were no significant differences in overall mortality or cause of death between treatment and placebo groups



Urogynecology

Pelvic Relaxation/Prolapse

Pelvic Relaxation/Prolapse

Protrusion of pelvic organs into or out of the vagina.

Etiology

- relaxation, weakness, or defect in the cardinal and uterosacral ligaments which normally maintain the uterus in an anteflexed position and prevent it from descending through the urogenital diaphragm (i.e. levator ani muscles)
- related to:
 - vaginal childbirth
 - aging
 - decreased estrogen (post-menopause)
 - following pelvic surgery
 - increased intra-abdominal pressure (obesity, chronic cough, constipation, ascites, heavy lifting)
 - congenital (rarely)
 - ethnicity (Caucasian women > Asian or African women)
 - collagen disorders

GENERAL CONSERVATIVE TREATMENT

(for pelvic relaxation/prolapse and urinary incontinence)

- Kegel exercises
- local vaginal estrogen therapy
- vaginal pessary

Table 12. Pelvic Prolapse

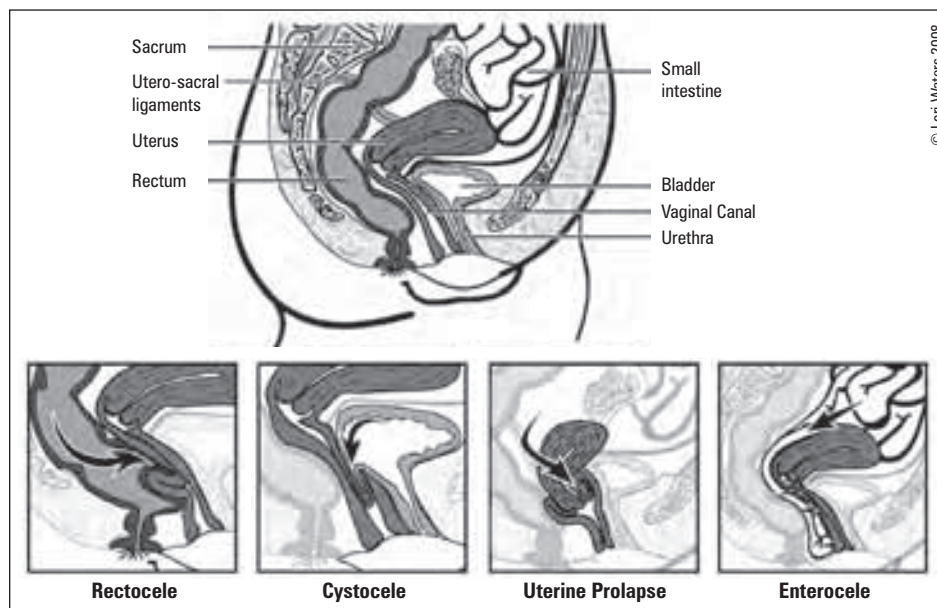
Type	Clinical Features	Treatment
Uterine Prolapse (Protrusion of cervix and uterus into vagina)	<ul style="list-style-type: none"> • Groin/back pain (stretching of uterosacral ligaments) • Feeling of heaviness/pressure in the pelvis <ul style="list-style-type: none"> • Worse with standing, lifting • Worse at the end of the day • Relieved by lying down • Ulceration/bleeding (particularly if hypoestrogenic) • \pm urinary incontinence 	<ul style="list-style-type: none"> • See <i>General Conservative Treatment</i>, above • Vaginal hysterectomy \pm surgical prevention of vault prolapse • Consider additional surgical procedures if urinary incontinence, cystocele, rectocele, and/or enterocele are present
Vault Prolapse (Protrusion of apex of vaginal vault into vagina, post-hysterectomy)		<ul style="list-style-type: none"> • See <i>General Conservative Treatment</i>, above • Sacralcolpopexy (vaginal vault suspension), sacrospinous fixation, or uterosacral ligament suspension
Cystocele (Protrusion of bladder into the anterior vaginal wall)	<ul style="list-style-type: none"> • Frequency, urgency, nocturia • Stress incontinence • Incomplete bladder emptying \pm associated increased incidence of urinary tract infections – may lead to renal impairment 	<ul style="list-style-type: none"> • See <i>General Conservative Treatment</i>, above • Anterior colporrhaphy ("anterior repair") • Consider additional/alternative surgical procedure if documented urinary stress incontinence
Rectocele (Protrusion of rectum into posterior vaginal wall)	<ul style="list-style-type: none"> • Straining/digitation to evacuate stool • Constipation 	<ul style="list-style-type: none"> • See <i>General Conservative Treatment</i>, above • Also laxatives and stool softeners • Posterior colporrhaphy ("posterior repair"), plication of endopelvic fascia and perineal muscles approximated in midline to support rectum and perineum (can result in dyspareunia)
Enterocele (Prolapse of small bowel in upper posterior vaginal wall)		<ul style="list-style-type: none"> • Similar to hernia repair • Contents reduced, neck of peritoneal sac ligated, uterosacral ligaments, and levator ani muscles approximated

**Grading of Pelvic Organ Prolapse**

- 0 = no descent during straining
- 1 = distal portion of prolapse > 1 cm above level of hymen
- 2 = distal portion of prolapse ≤ 1 cm above or below level of hymen
- 3 = distal portion of prolapse > 1 cm below level of hymen but without complete vaginal eversion
- 4 = complete eversion of total length of lower genital tract
- **Procidentia:** failure of genital supports and complete protrusion of uterus through the vagina



The only **true** hernia of the pelvis is an **ENTEROCELE** because peritoneum herniates with the small bowel.

**Figure 14. Pelvic Prolapse**



Urinary Incontinence

- see Urology, U5

Stress Incontinence

Involuntary loss of urine with increased intra-abdominal pressure (coughing, laughing, sneezing, walking, running).

The gold standard diagnostic test for urinary incontinence is multichannel urodynamics. A large proportion of cases are correctly diagnosed from clinical history alone and this can be supplemented with patient urinary and intake diaries.

Health Technol Assess 2006; 10(6):1-132.

STRESS INCONTINENCE

Risk Factors for Stress Incontinence in Women

- pelvic prolapse
- pelvic surgery
- vaginal delivery
- hypoestrogenic state (post-menopause)
- age
- smoking
- neurological/pulmonary disease

Treatment

- see *General Conservative Treatment*, GY35
- surgical
 - tension-free vaginal tape (TVT), tension-free obturator tape (TOT), prosthetic/fascial slings or retropubic bladder suspension (Burch or Marshall-Marchetti-Krantz procedures)

Urge Incontinence

Urine loss associated with an abrupt, sudden urge to void.



Rule Out Neurological Causes of Urge Incontinence

Multiple sclerosis
Slipped disc
Diabetes mellitus

URGE INCONTINENCE

Definition

- urine loss associated with an abrupt, sudden urge to void
- “overactive bladder”
- diagnosed based on symptoms

Etiology

- idiopathic (90%)
- detrusor muscle overactivity (“detrusor instability”)

Associated Symptoms

- frequency, urgency, nocturia, leakage

Treatment

- behaviour modification (reduce caffeine/liquid, smoking cessation, regular voiding schedule)
- Kegel exercises
- medications
 - anticholinergics – oxybutinin (Ditropan®), tolterodine (Detrol®)
 - tricyclic antidepressants – imipramine



Gynecological Oncology

Uterus

ENDOMETRIAL CARCINOMA

Epidemiology

- most common gynecological malignancy in North America (40%); 4th most common cancer in women
- 2-3% of women develop endometrial carcinoma during lifetime
- mean age is 60 years
- majority are diagnosed in early stage due to detection of symptoms
- 85-90% 5-year survival for stage I disease
- overall 5-year survival for all stages is 70-80%

Classification

- Type I – endometrioid adenocarcinoma (~80% of cases)
- Type II – serous, clear cell carcinomas (~15% of cases)



Incidence of Malignant Gynecological Lesions in North America
endometrium > ovary > cervix > vulva
> vagina > fallopian tube

Risk Factors

- Type I: excess estrogen (estrogen unopposed by progesterone)
 - obesity
 - PCOS
 - unbalanced HRT (balanced HRT is actually protective)
 - nulliparity
 - late menopause
 - estrogen-producing ovarian tumours (e.g. granulosa cell tumours)
 - HNPCC (hereditary non-polyposis colorectal cancer)/Lynch II syndrome
 - tamoxifen
- Type II: not estrogen related
 - possibly tamoxifen

Clinical Features

- Type I: postmenopausal bleeding in majority, abnormal uterine bleeding in majority of affected pre-menopausal women (menorrhagia, intermenstrual bleeding)
- Type II: may not present with bleeding in early stage, more likely to present with advanced stage disease with symptoms like ovarian cancer (i.e. bloating, bowel dysfunction, pelvic pressure)

Table 13. FIGO Staging of Endometrial Cancer

Stage	Description	Stage	Description
I	Confined to corpus	IV	Invasion of bladder \pm bowel mucosa \pm distant metastases
IA	No or less than half myometrial invasion	IVA	Invasion of bladder \pm bowel mucosa
IB	Invades through \geq one half of myometrium	IVB	Distant mets, including intra-abdominal mets \pm inguinal LNs
II	Tumour invades cervical stroma, but does not extend beyond uterus*		
III	Local and/or regional spread of the tumour		
IIIA	Invasion of serosa, corpus uteri \pm adnexae		
IIIB	Vaginal \pm parametrial involvement		
IIIC	Metastasis to pelvic \pm para-aortic LNs		
IIIC1	Positive pelvic LN		
IIIC2	Positive para-aortic LN \pm positive pelvic LNs		

FIGO: International Federation of Gynecology and Obstetrics

*Note: endocervical glandular involvement is now considered as Stage I (previously Stage II)

Investigations

- endometrial sampling:
 - office endometrial biopsy
 - D&C \pm hysteroscopy
- \pm pelvic ultrasound (in women where adequate endometrial sampling not feasible without invasive methods)
 - not acceptable as alternative to pelvic exam or endometrial sampling to rule out cancer

Spread

- most common is direct extension
- lymphatic spread to pelvic and para-aortic nodes
- transubal dissemination to peritoneal cavity
- hematogenous spread (usually to lungs, liver)

Treatment

- surgical: hysterectomy/bilateral salpingo-oophorectomy (BSO) and pelvic washings \pm pelvic and para-aortic node dissection \pm omentectomy
 - goals: diagnosis, staging, treatment, defining optimal adjuvant treatment
 - laparoscopic approach associated with improved quality of life (optimal for most patients)
- adjuvant radiotherapy (for improved local control in patients at risk for local recurrence) and adjuvant chemotherapy (in patients at risk for distant recurrence or with metastatic disease) – based on presence of poor prognostic factors in definitive pathology
- chemotherapy often used for recurrent disease (especially if high grade or aggressive histology)
- hormonal therapy: progestins can be used for recurrent disease (especially if low grade)

UTERINE SARCOMA

- rare: 2-6% of all uterine malignancies
- arise from stromal components (endometrial stroma, mesenchymal or myometrial tissues)
- behave more aggressively and are associated with poorer prognosis than endometrial carcinoma; 5-year survival – 35%
- vaginal bleeding is most common presenting symptom

**Risk Factors for Endometrial Cancer****COLD NUT**

Cancer (ovarian, breast, colon)

Obesity

Late menopause

Diabetes mellitus

Nulliparity

Unopposed estrogen: PCOS, anovulation, HRT

Tamoxifen: chronic use



Postmenopausal bleeding = endometrial cancer until proven otherwise.
95% present with vaginal bleeding.



An endometrial thickness of 5 mm or more is considered abnormal in a postmenopausal woman with vaginal bleeding.

True Pelvis

Area of pelvis between pelvic inlet and outlet, i.e. it does not include the abdominal contents in the pelvis found above the pelvic inlet.

**Prognostic Factors**

1. Grade (histological differentiation)
2. Vascular, lymphatic involvement
3. Progesterone-receptor levels
4. Myometrial invasion

**Uterine Sarcoma – Symptoms****BAD-P**

Bleeding

Abdominal distention

Foul smelling vaginal Discharge

Pelvic Pressure

1. Mixed Müllerian Mesodermal Tumour (Carcinosarcoma)

- most common type of uterine sarcoma (43%)
- both epithelial and sarcomatous malignant elements are present
- tend to form bulky polypoid masses that often fill the uterine cavity and extend into or through the endocervical canal – often have extrauterine disease at presentation

Treatment

- usually treated as “very high grade endometrial carcinoma” since behaviour and treatment similar (i.e. surgical staging, adjuvant chemotherapy and radiation)

2. Leiomyosarcoma

- account for one third of uterine sarcomas
- when occurs, often coexists with benign leiomyomata (fibroids)
- 50% of time, leiomyosarcomata arise within a fibroid (“sarcomatous degeneration”)
- average age of presentation is 55 years but may present in pre-menopause
- histologic distinction from leiomyoma
 - increased mitotic count (>10 mitoses/10 high power fields)
 - tumour necrosis
 - cellular atypia
- often diagnosed postoperatively after uterus removed for presumed fibroids

Clinical Features

- “rapidly” enlarging fibroids in a pre-menopausal woman
- enlarging fibroids in a postmenopausal woman

Treatment

- hysterectomy/BSO usually without node dissection due to high propensity for vascular spread (i.e. liver/lung metastases)
- adjuvant chemotherapy may be used if tumour has spread beyond uterus, for palliation
- radiation therapy does not improve local control or survival
- poor outcome overall, even for early stage disease

3. Endometrial Stromal Sarcoma

- usually presents in perimenopausal or postmenopausal women with abnormal uterine bleeding
- diagnosed by histology of endometrial biopsy or D&C

Treatment

- hysterectomy/BSO (ALWAYS remove ovaries as ovarian hormones may stimulate growth)
- adjuvant therapy based on stage and histologic features (hormones and/or radiation)
- hormonal therapy (progestins) may be used for metastatic disease in low grade ESS



A rapidly enlarging uterus, especially in a postmenopausal woman, should prompt consideration of leiomyosarcoma.



Ovary

BENIGN OVARIAN TUMOURS

- see Table 14
- most are asymptomatic
- usually enlarge slowly, if at all
- may rupture or undergo torsion, causing pain
- pain associated with torsion of an adnexal mass usually originates in the iliac fossa and radiates to the flank
- peritoneal irritation may result from an infarcted tumour – rare

MALIGNANT OVARIAN TUMOURS

- see Table 14

Epidemiology

- lifetime risk 1.4% (1/70)
- in women >50 years, more than 50% of ovarian tumours are malignant
- causes more deaths in North America than all other gynecologic malignancies combined
- 4th leading cause of cancer death in women
- 65% epithelial; 35% non-epithelial
- 5-10% of epithelial ovarian cancers are related to hereditary predisposition



Ovarian Tumour Markers

Epithelial cell – CA-125

Stromal

Granulosa cell – inhibin

Sertoli-Leydig – androgens

Germ cell

Dysgerminoma – LDH

Yolk sac – AFP

Choriocarcinoma – beta-hCG

Immature Teratoma – none

Embryonal cell – AFP + beta-hCG

Risk Factors (for **epithelial** ovarian cancers)

- nulliparity
- early menarche/late menopause
- age
- family history of breast, colon, endometrial, ovarian cancer
- race: Caucasian

Protective Factors (for **epithelial** ovarian cancers)

- OCP: likely due to ovulation suppression (significant reduction in risk even after 1 year of use)
- pregnancy/breastfeeding
- tubal ligation (recently questioned)
- hysterectomy (without removal of ovaries)
- bilateral salpingo-oophorectomy (prophylactic surgery performed for this reason in women with known high risk – i.e. BRCA mutation carriers)

Clinical Features

- most women with epithelial ovarian cancer present with advanced stage disease since often “asymptomatic” until disseminated disease
 - vague non-specific symptoms associated with early stage disease
- when present, non-specific symptoms may include:
 - vague abdominal symptoms (nausea, bloating, dyspepsia, anorexia, early satiety)
 - symptoms of mass effect
 - ♦ increased abdominal girth – from ascites or tumour itself
 - ♦ urinary frequency
 - ♦ constipation
 - ♦ fluid wave – signs of ascites
 - postmenopausal bleeding; irregular menses if pre-menopausal (rare)

Low Malignant Potential (also called “Borderline”) Tumours

- pregnancy, OCP and breastfeeding are found to be protective factors
- ~15% of all epithelial ovarian tumours
- tumour cells display malignant characteristics histologically, but no invasion is identified
- able to metastasize, but not commonly
- treated primarily with surgery (BSO/omental biopsy ± hysterectomy)
 - NO proven benefit of chemotherapy
- generally slow growing, excellent prognosis
 - 5-year survival >99%
 - recurrences tend to occur late, may be associated with low grade serous carcinoma

**Risk/Protective Factors for Epithelial Ovarian Cancer****NO CHILD**

Nulliparity
OCP, breast-feeding, tubal ligation, hysterectomy (protective)
Caucasian
Family History
Increasing age (>40)
Late menopause
Delayed child-bearing



Any adnexal mass in postmenopausal women should be considered malignant until proven otherwise.



Most (70%) epithelial ovarian cancers present at stage III disease.



Diagnosis requires surgical pathology.

Table 14. Ovarian Tumours



Type	Description	Presentation	Ultrasound/Cytology	Treatment
FUNCTIONAL TUMOURS (all benign)				
Follicular cyst 	Follicle fails to rupture during ovulation	Usually asymptomatic May rupture, bleed, tort, infarct causing pain ± signs of peritoneal irritation	4-8 cm mass, unilocular, lined with granulosa cells	Symptomatic or suspicious masses warrant surgical exploration Otherwise if <6 cm, wait 6 weeks then re-examine as cyst usually regresses with next cycle OCP (ovarian suppression) – will prevent development of new cysts Treatment usually laparoscopic
Lutein cyst	Corpus luteum fails to regress after 14 days, becoming cystic or hemorrhagic	More likely to cause pain than follicular cyst May delay onset of next period	Larger (10-15 cm) and firmer than follicular cysts	Same as for follicular cysts
Theca-lutein cyst	Due to atretic follicles stimulated by abnormal β-hCG levels	Associated with molar pregnancy, ovulation induction with clomiphene		Conservative Cyst will regress as β-hCG levels fall
Luteoma of pregnancy	Usually bilateral Due to prolonged elevation of β-hCG	Associated with multiple pregnancy		Same as for theca-lutein Regresses postpartum
Endometrioma	See <i>Endometriosis</i> , GY15			
Polycystic Ovaries	See <i>PCOS</i> , GY23			
BENIGN GERM-CELL TUMOURS				
Benign cystic teratoma (dermoid) 	Single most common ovarian germ cell neoplasm Elements of all 3 cell lines, contains dermal appendages (sweat and sebaceous glands, hair follicles, teeth)	May rupture, twist, infarct 20% bilateral 20% occur outside of reproductive years	Smooth-walled, mobile, unilocular Ultrasound may show calcification which is pathognomonic	Treatment usually laparoscopic cystectomy; may recur

Table 14. Ovarian Tumours (continued)

Type	Description	Presentation	Ultrasound/Cytology	Treatment
MALIGNANT GERM-CELL TUMOURS				
General Information	Rapidly growing, 2-3% of all ovarian cancers	Usually children and young women (<30 years)		Surgical resection (often conservative unilateral salpingo-oophorectomy ± nodes) ± chemo
Dysgerminoma	Produces lactate dehydrogenase (LDH)	10% bilateral		Usually very responsive to chemotherapy, therefore complete resection is not necessary for cure
Immature teratoma	No tumour marker identified			
Yolk sac tumour	Produces alpha fetoprotein (AFP) Rare	Unilateral		More aggressive subtype, often need chemo (BEP)
Embryonal	Produces AFP and β-hCG			
Carcinoma	Rare			
Choriocarcinoma	Produces β-hCG			
EPITHELIAL OVARIAN TUMOURS (may be benign, malignant or borderline)				
General Information	Derived from mesothelial cells lining peritoneal cavity Classified based on histologic type 80-85% of all ovarian neoplasms (includes malignant)		Varies depending on subtype	Benign Cystectomy vs. unilateral salpingo-oophorectomy Malignant 1. Early stage (stage 1): BSO ± hysterectomy ± omentectomy ± peritoneal washings ± staging (peritoneal biopsies + node dissection) ± adjuvant chemotherapy 2. Advanced stage: Upfront cytoreductive (debulking) surgery vs. neoadjuvant chemotherapy Adjuvant chemotherapy: IP chemotherapy vs. IV Carbo/Taxol
Serous	Most common ovarian tumour 50% of all ovarian cancers 75% of epithelial tumours 70% benign	20-30% bilateral	Lining similar to fallopian tube epithelium Often multilocular Histologically contain Psammoma bodies (calcified concentric concretions)	
Mucinous	85% benign 20% of epithelial tumours	Rarely complicated by <i>Pseudomyxoma peritonei</i> : implants seed abdominal cavity and produce large quantities of mucin	Resembles endocervical epithelium Often multilocular May reach enormous size	Query poor response to chemotherapy Unclear role for radiation in patients with no residual disease (rare) If mucinous – remove appendix as well
Endometrioid	20% of epithelial ovarian Ca High malignant potential		Histology resembles endometrium	
Clear cell	≤1% of epithelial ovarian Ca High malignant potential		Histology resembles mesonephric cells	
Brenner tumour	≤1% of epithelial ovarian Ca Majority benign		Fibrotic tumour with transitional cell-like epithelial core	
SEX CORD STROMAL OVARIAN TUMOURS				
General Information				Surgical resection of tumour Chemotherapy may be used for metastatic disease not resectable
Fibroma (benign)	From mature fibroblasts in ovarian stroma	Non-functioning Occasionally associated with Meig's syndrome	Firm, smooth rounded tumour with interlacing fibrocytes	
Granulosa-theca cell tumours (benign or malignant)	Can be associated with endometrial cancer Inhibin is tumour marker	Estrogen-producing → feminizing effects (precocious puberty, menorrhagia, postmenopausal bleeding)	Histologic hallmark of cancer is small groups of cells known as Call-Exner bodies	
Sertoli-Leydig cell tumour (benign or malignant)	Can measure elevated androgens as tumour markers	Androgen-producing → virilizing effects (hirsutism) deep voice, recession of front hairline)		
METASTATIC OVARIAN TUMOURS				
From GI tract, breast, endometrium, lymphoma	4-8% of ovarian malignancies		Krukenberg tumour = metastatic ovarian tumour from other site (usually GI tract, commonly stomach or colon, breast) with "signet-ring" cells	

Investigation of Suspicious Ovarian Mass

- goals of management: address symptoms and optimal surgical staging of malignancy
- women with suspected ovarian cancer based on history, physical, or investigations should be referred to a gynecologic oncologist prior to surgery to facilitate optimal surgery
 - bimanual examination
 - solid, irregular, or fixed pelvic mass is suggestive of ovarian cancer
 - RMI (Risk of Malignancy Index) is best tool available to assess likelihood of ovarian malignancy and need for pre-operative gynaecologic oncology referral (see sidebar)
- bloodwork: CA-125 for baseline, CBC, liver function tests, electrolytes, creatinine
- radiology: transvaginal U/S best to visualize ovaries; CT scan abdomen and pelvis best to look for metastatic disease
- bone scan or PET scan **not** indicated
- try to rule out other primary source if suspected based on:
 - occult blood per rectum: if positive, endoscopy ± barium enema
 - if gastric symptoms, gastroscopy ± upper GI series
 - if abnormal vaginal bleeding, endometrial biopsy to rule out concurrent endometrial cancer, colposcopy ± ECC to rule out cervical cancer if abnormal cervix
 - mammogram if breast lesion identified or risk factors present

Screening

- no effective method of mass screening
- routine CA-125 level measurements or U/S **not** recommended
 - more women suffer from false positive results than helped
- controversial in high risk groups – starting age 30, transvaginal U/S and CA-125 (no consensus on interval)
 - familial ovarian cancer (>1 first degree relative affected, BRCA-1 mutation)
 - other cancers (i.e. endometrial, breast, colon)
 - BRCA-1 or BRCA-2 mutation: may recommend prophylactic bilateral oophorectomy after age 35 or when child-bearing is completed

Table 15. FIGO Staging for Primary Carcinoma of the Ovary (Surgical Staging)

Stage	Description
I	Growth limited to the ovaries
IA	1 ovary, no ascites, no tumour on external surface, capsule intact
IB	2 ovaries, no ascites, no tumour on external surface, capsule intact
IC	1 or 2 ovaries with any of the following: capsule ruptured, tumour on ovarian surface or malignant cells in ascites
II	Growth involving one or both ovaries with pelvic extension
IIA	Extension ± metastases to uterus/tubes
IIB	Extension to other pelvic structures
IIC	II A/B with malignant cells in ascites or positive peritoneal washings
III	Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver mets is Stage III.
IIIA	Microscopic peritoneal metastasis beyond pelvis, LNs negative
IIB	Macroscopic peritoneal metastasis beyond pelvis <2 cm, LNs negative
IIC	Implant >2 cm and/or retroperitoneal or inguinal nodes
IV	Distant metastasis beyond peritoneal cavity

FIGO: International Federation of Gynecology and Obstetrics

Risk of Malignancy Index (RMI)

Moore et. al. *Am J Obst Gynecol.* May 2010.

$$RMI = U \times M \times CA-125$$

ULTRASOUND FINDINGS (1 pt for each)

- Multilocular cyst
- Evidence of solid areas
- Evidence of metastases
- Presence of ascites
- Bilateral lesions
- U = 1 (for U/S scores of 0 or 1)
- U = 4 (for U/S scores of 2-5)

MENOPAUSAL STATUS

- Postmenopausal: M = 4
- Pre-menopausal: M = 1

ABSOLUTE VALUE OF CA-125 SERUM LEVEL

For RMI > 200: Gynecologic Oncology referral is recommended



Causes of Elevated CA-125

- Age influences reliability of test as a tumour marker
- 50% sensitivity in early stage ovarian cancer (poor) – therefore not good for screening

MALIGNANT

- Gyne: ovary, uterus
- Non-Gyne: pancreas, stomach, colon, rectum

NON MALIGNANT

- Gyne: benign ovarian neoplasm, endometriosis, pregnancy, fibroids, PID
- Non-Gyne: cirrhosis, pancreatitis, renal failure



CA-125 is indicated for monitoring response to treatment.



Malignant Ovarian Tumour Prognosis

5-year Survival

- Stage I: 75-95%
- Stage II: 60-75%
- Stage III: 23-41%
- Stage IV: 11%

Cervix

BENIGN CERVICAL LESIONS

- Nabothian cyst/inclusion cyst
 - no treatment required
- endocervical polyps
 - treatment is polypectomy (office procedure)

MALIGNANT CERVICAL LESIONS

- majority are squamous cell carcinomas (95%), adenocarcinomas increasing (5%), rare subtypes include small cell, adenosquamous
- 8,000 deaths annually in North America
- annual Pap test reduces a woman's chance of dying from cervical cancer from 0.4% to 0.05%
- average age: 52 years old

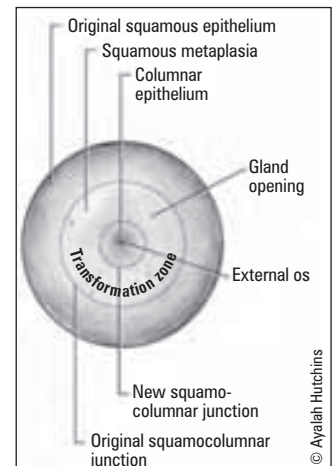


Figure 15. The Cervix



Cervical cancer is caused by HPV infection.

Systematic Review of RCTs for HPV Vaccination Prophylactic Vaccination Against Human Papillomavirus Infection in Women: A Systematic Review of Randomized Controlled Trials

Rambout L, Hopkins L, Fung Kee Fung M, et al. *CMAJ* 2007; 177

Purpose: To assess the effectiveness of HPV vaccination for preventing HPV infection and precancerous cervical lesions.

Study: Systematic review of studies of prophylactic HPV vaccination.

Data Sources: MEDLINE, EMBASE, Cochrane Central Registry of Controlled Trials, and the Cochrane Library.

Patients: Of 457 studies, nine were included in the review (six of these were RCTs). A total of 40,323 females were enrolled. All participants had received HPV vaccinations that included coverage of the HPV 16 strain.

Main outcomes: Frequency of high-grade cervical lesions, persistent HPV infection, low-grade cervical lesions, external genital lesions, adverse events, and death.

Results: HPV vaccination was associated with a reduction in the frequency of high-grade cervical lesions caused by vaccine-type HPV strains compared with control groups. The HPV vaccination was also found to be efficacious in reducing persistent HPV infection, low-grade lesions, and genital warts.

Conclusion: Prophylactic vaccination of women between 15-25 years not previously infected with vaccine-type HPV strains, has been found to be efficacious in preventing HPV infection and precancerous cervical lesions.

Liquid-based Cytologic Smear vs. Conventional Pap Smear

Am J Obstet Gynecol 2001; 185(2):308-17

Purpose: To assess the cytologic diagnosis and sample adequacy of liquid-based cervical cytologic smear (ThinPrep) versus conventional Papanicolaou smear.

Study: Systematic review of prospective trials comparing ThinPrep and conventional Pap smears.

Data sources: MEDLINE, PubMed, Silver Platter were searched for literature published in English between January 1990 and April 2000. Selection criteria included split-sample (SS) and direct-to-vial (DV) (case-cohort) studies.

Patients: 25 studies met the selection criteria (n=533,039 women; 221,864 in ThinPrep group; 378,659 in conventional smear group; 67,484 in both groups)

Main outcomes: (i) Frequency of diagnoses of ASCUS, LSIL, HSIL. (ii) Adequacy of sample collection (contains squamous cells, endocervical cells, and possibly metaplastic cells).

Results: Liquid-based smears (ThinPrep) had significantly improved cytologic diagnosis of LSIL (OR = 1.27 to 2.15) and diagnosis of HSIL (OR = 2.26), but no difference in rate of diagnosis of ASCUS (OR = 1.03). Liquid-based pap smear also resulted in improved sample adequacy (OR = 1.64 to 2.11).

Conclusion: Liquid-based cytologic smears resulted in better diagnosis of cervical premalignant lesions (HSIL and LSIL) and improved sample adequacy, compared to conventional Pap smears.

Etiology

- at birth, vagina is lined with squamous epithelium; columnar epithelium lines only the endocervix and the central area of the ectocervix (original squamocolumnar junction)
- during puberty, estrogen stimulates eversion of a single columnar layer (ectopy), thus exposing it to the acidic pH of the vagina, leading to metaplasia (change of exposed epithelium from squamous to columnar)
 - a new squamocolumnar junction forms as a result
- the transformation zone (TZ) is the area located between the original and the current squamocolumnar junction (Figure 15)
- the majority of dysplasias and cancers arise in the TZ of the cervix
- must have active metaplasia in presence of inducing agent (HPV) to get dysplasia
- dysplasia → carcinoma in situ (CIS) → invasion
- slow process (~10 years on average)
- growth is by local extension
- metastasis occurs late

Risk Factors

- HPV infection
 - see *Sexually Transmitted Infections*, GY26
 - high risk of neoplasia associated with types 16, 18
 - low risk of neoplasia associated with types 6, 11
 - >99% of cervical cancers contain one of the high risk HPV types
- smoking
- high risk behaviours (risk factors for HPV infection)
 - multiple partners
 - other STIs (HSV, trichomonas)
 - early age first intercourse
 - high risk male partner
- poor screening uptake is the most important risk factor for cervical cancer in Canada
- at-risk groups include:
 - immigrant Canadians
 - First Nations Canadians
 - geographically isolated Canadians
 - sex-trade workers
 - low socioeconomic status

Prevention: Quadrivalent HPV Recombinant Vaccine (Gardasil®)

- currently indicated for females 9 to 26 years of age for prevention of diseases caused by HPV types 6, 11, 16 and 18 (genital warts, cervical, vulvar and vaginal dysplasias and cancers)
- for optimal benefit of vaccination, should be administered before onset of sexual activity (i.e. before exposure to virus)
- administered IM at time 0, 2 and 6 months, may be given at the same time as Hep B or other vaccines using a different injection site
- not for treatment of active infections
- most women will not be infected with all four types of the virus at the same time, therefore vaccine is still indicated for sexually active females or those with a history of previous HPV infection or HPV-related disease
- conception should be avoided until 30 days after last dose of vaccination
- side effects: pain, swelling, erythema, low grade fever
- contraindications: pregnant women and women who are nursing (limited data)

Clinical Features

- squamous cell carcinoma (SCC)
 - exophytic, fungating tumour
- adenocarcinoma
 - endophytic, with barrel-shaped cervix
- early
 - asymptomatic
 - discharge: initially watery, becoming brown or red
 - post-coital bleeding
- late
 - 80-90% present with bleeding: either post-coital, postmenopausal or irregular bleeding
 - pelvic or back pain (extension of tumour to pelvic walls)
 - bladder/bowel symptoms
- signs
 - friable, raised, reddened or ulcerated area visible on cervix

Cervical Screening Guidelines (Pap Test)

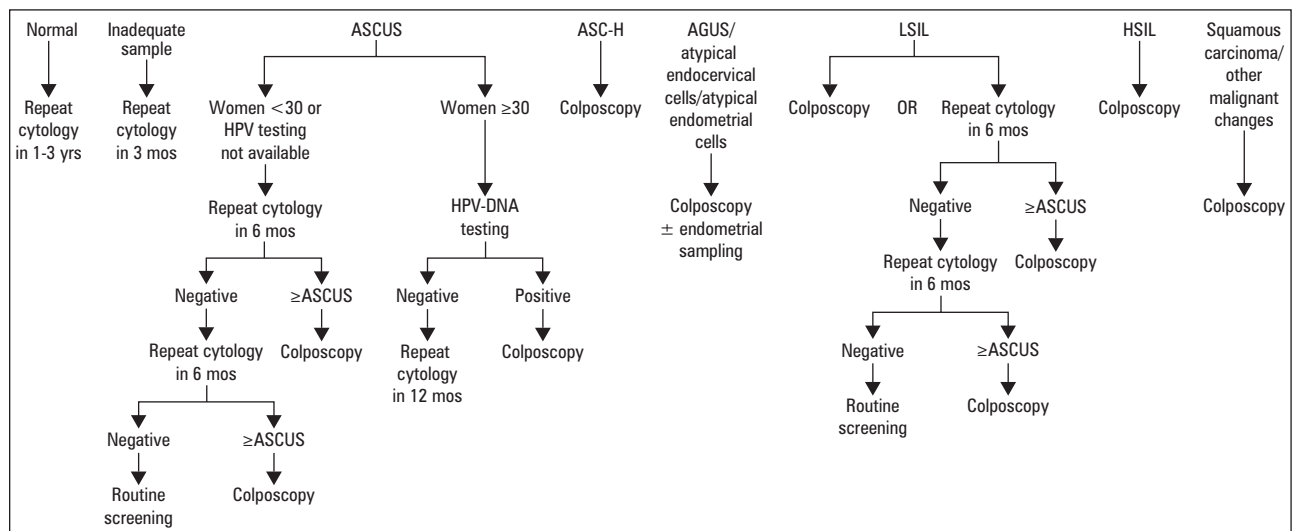
- endocervical and exocervical cell sampling (aim is to sample the TZ)
- best identifies squamous cell abnormalities, less reliable for glandular abnormalities
 - false positives 5-10%, false negatives 10-40% (for single test)
 - false negative rate 50% for existing cervical cancer
- all women: start annual screening at age 21, or 3 years after onset of vaginal intercourse
 - women ≥ 30 years: if 3 normal Paps in a row, and no previous abnormal Paps, can get screened every 2-3 years (if adequate recall mechanism in place)
 - women ≥ 70 years: if 3 normal Paps in a row and no abnormal Paps in last 10 years, can discontinue screening (if remain at low risk)
- pregnant women and women who have sex with women should follow the routine cervical screening regimen
- women who have had a hysterectomy:
 - total: discontinue screening if hysterectomy was for benign disease and no history of cervical dysplasia or HPV infection
 - subtotal: continue screening according to guidelines
- exceptions to guidelines:
 - immunocompromised (transplant, steroids, DES exposure)
 - HIV and high risk
 - previously unscreened patients

Table 16. Cytological Classification

Bethesda Grading System	Classic System/ Cervical Intraepithelial Neoplasia (CIN) Grading System
Within normal limits	Normal
Infection	Inflammatory atypia (organism)
Reactive and reparative changes	
Squamous cell abnormalities	
Atypical squamous cells of undetermined significance (ASCUS)	Squamous atypia of uncertain significance
Atypical squamous cells, cannot exclude HSIL (ASC-H)	
Low grade squamous intraepithelial lesion (LSIL)	HPV atypia or mild dysplasia (CIN I)
High grade squamous intraepithelial lesion (HSIL)	Moderate dysplasia (CIN II)
	Severe dysplasia (CIN III)
	Carcinoma in situ (CIS)
Squamous cell carcinoma (SCC)	Squamous cell carcinoma (SCC)
Glandular cell abnormalities	
Atypical glandular cells of undetermined significance (AGUS)	Glandular atypia of uncertain significance
Endocervical adenocarcinoma	Adenocarcinoma
Endometrial adenocarcinoma	
Extrauterine adenocarcinoma	
Adenocarcinoma, not otherwise specified (NOS)	



The Bethesda Classification System is based on cytological results of a Pap test that permits the examination of cells but not tissue structure. The diagnosis of cervical intraepithelial neoplasia (CIN) or cervical carcinoma requires a tissue sample, obtained by biopsy of suspicious lesions (done during colposcopy), to make a histologic diagnosis.

**Figure 16. Decision Making Chart for Pap Test (not applicable for adolescents)**

Adapted from Ontario Cervical Screening Practice Guidelines, June 2005. Cervical screening guidelines unique to each province.

Diagnosis

- see *Colposcopy*, GY9
- apply acetic acid and identify acetowhite lesions, punctation, mosaicism, and abnormal blood vessels to guide cervical biopsy
- endocervical curettage (ECC) if entire lesion is not visible or no lesion visible
- diagnostic excision (loop electrosurgical excision procedure, LEEP) if:
 - lesion extends into endocervical canal
 - positive ECC
 - discrepancy between Pap test results and colposcopy
 - microinvasive carcinoma
- consider cold knife conization (in OR) if glandular abnormality suspected based on cytology or colposcopic findings due to concern for margin interpretation
- tests permitted for FIGO clinical staging include: physical exam (including EUA), cervical biopsy (including cone biopsy), proctoscopy/cystoscopy, IVP, ultrasound liver/kidneys, CXR, LFTs
- MRI and/or CT and/or PET scan often done to facilitate planning of radiation therapy, results do not influence clinical stage

Table 17. FIGO Staging Classification of Cervical Cancer (clinical staging)

Stage	Description
I	Confined to cervix
IA	Microinvasive (diagnosed only by microscopy)
IA ₁	Stromal invasion not >3 mm deep, not >7 mm wide
IA ₂	3-5 mm deep; not >7 mm wide
IB	Clinically visible lesion confined to cervix, or microscopic lesion >IA
IB ₁	Clinically visible lesion ≤4 mm in greatest dimension
IB ₂	Clinically visible lesion >4 mm in greatest dimension
II	Beyond uterus but not to the pelvic wall or lower 1/3 of vagina
IIA	No obvious parametrial involvement
IIA ₁	Clinically visible lesion ≤4 mm in greatest dimension
IIA ₂	Clinically visible lesion >4 mm in greatest dimension
IIB	Obvious parametrial involvement
III	Extends to pelvic wall, and/or involves lower 1/3 of vagina and/or causes hydronephrosis or non-functioning kidney
IIIA	Involves lower 1/3 vagina but no extension into pelvic side wall
IIIB	Involves lower 1/3 vagina and extends into pelvic side wall and/or hydronephrosis or non-functioning kidney
IV	Carcinoma has extended beyond true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum
IVA	Spread of the growth to adjacent organs
IVB	Distant metastases

Table 18. Treatment of Patients with Cervical Dysplasia and Cervical Cancer

	Treatment
CIN I (LSIL)	Observe with regular cytology (every 6 months) Many lesions will regress or disappear (60%) Colposcopy if positive on 2 consecutive smears Lesions which progress should have area excised by either LEEP, laser, cryotherapy or cone biopsy (with LEEP, tissues obtained for histological evaluation)
CIN II and CIN III (HSIL)	Colposcopy referral Ablation or excision therapy: LEEP, laser, cryotherapy, cone excision, cautery Hysterectomy – only if no desire for future childbearing
Stage IA ₁ (=microinvasive SCC if: <3 mm invasion and no CLS)	Cervical conization if future fertility desired Simple hysterectomy if future fertility is not desired
Stage IA ₂ , IB ₁	Typically treated with radical hysterectomy and pelvic lymphadenectomy (sentinel nodes under study) Advantage is that ovaries can be spared if pre-menopausal For fertility preservation, may have radical trachelectomy and nodes instead of radical hysterectomy for early-stage disease Concurrent chemoradiation therapy if adverse prognostic factors on radical surgical specimen, poor surgical candidate, or if significantly adverse prognostic factors present at time of diagnosis
Stages IB ₂ (>4 cm), II, III, IV	Concurrent chemoradiation therapy

Abnormal Pap Tests in Pregnancy

- incidence – 1/2,200
- Pap test at all initial prenatal visits
 - if abnormal Pap or suspicious lesion, refer to colposcopy
- if diagnostic conization required, should be deferred until second trimester (T2) to minimize risk of pregnancy loss
- if invasive cancer ruled out, management of dysplasia deferred until after completion of pregnancy (may deliver vaginally)



Cervical cancer is most prevalent in developing countries and therefore is the only gynecologic cancer that uses clinical staging. This facilitates consistent international staging with countries that do not have technologies such as CT and MRI.



Cervical Cancer Prognosis

5 Year Survival

- Stage 0: 99%
- Stage I: 75%
- Stage II: 55%
- Stage III: 30%
- Stage IV: 7%
- Overall: 50-60%

- if invasive cancer present, management depends on prognostic factors, degree of fetal maturity, and patient wishes
 - general recommendations in T1: consider pregnancy termination, management with either radical surgery (hysterectomy vs. trachelectomy if desires future fertility) or concurrent chemoradiation therapy
 - recommendations in T2/T3: delay of therapy until viable fetus and C/S for delivery with concurrent radical surgery or subsequent concurrent chemoradiation therapy

Vulva



BENIGN VULVAR LESIONS

Non-Neoplastic Disorders of Vulvar Epithelium

- biopsy is necessary to make diagnosis and/or rule out malignancy
- **hyperplastic dystrophy** (squamous cell hyperplasia)
 - surface thickened and hyperkeratotic
 - pruritus most common symptom
 - typically postmenopausal women
 - treatment: 1% fluorinated corticosteroid ointment bid for 6 weeks
- **lichen sclerosis**
 - subepithelial fat becomes diminished, labia become thin and atrophic, membrane-like epithelium, labial fusion
 - pruritus, dyspareunia, burning
 - 'figure of 8' distribution
 - most common in postmenopausal women but can occur at any age
 - treatment: ultrapotent topical steroid 0.05% clobetasol x 2-4wks then taper down
- **mixed dystrophy** (lichen sclerosis with epithelial hyperplasia)
 - hyperkeratotic areas with areas of thin, shiny epithelium
 - treatment: fluorinated corticosteroid ointment



Any suspicious lesion of the vulva should be biopsied.

Tumours

- papillary hidradenoma, nevus, fibroma, hemangioma

MALIGNANT VULVAR LESIONS

Epidemiology

- 5% of genital tract malignancies
- 90% squamous cell carcinoma; remainder melanomas, basal cell carcinoma, Paget's disease, Bartholin's gland carcinoma
 - Type I disease: HPV-related disease (50-70%)
 - ♦ more likely in younger women
 - ♦ 90% of vulvar intraepithelial neoplasia (VIN) contain HPV DNA (usually types 16, 18)
 - Type II disease: not HPV-related, associated with current or previous vulvar dystrophy
 - ♦ usually postmenopausal women

Risk Factors

- HPV infection (see above)
- VIN (vulvar intraepithelial neoplasia): precancerous change which presents as multicentric white or pigmented plaques on vulva (may only be visible at colposcopy)
 - progression to cancer rarely occurs with appropriate management
 - treatment: local excision (i.e. superficial vulvectomy ± split thickness skin grafting to cover defects [if required]) vs. ablative therapy (i.e. laser, cauterization) vs. local immunotherapy (imiquimod)

Clinical Features

- many patients asymptomatic at diagnosis (many also deny or minimize symptoms)
- most lesions occur on the labia majora, followed by the labia minora (less commonly on the clitoris or perineum)
- localized pruritus or lesion most common
- less common: raised red, white or pigmented plaque, ulcer, bleeding, discharge, pain, dysuria
- patterns of spread
 - local
 - groin lymph nodes (usually inguinal → pelvic nodes)
 - hematogenous

Investigations

- physical examination
- ± colposcopy
- ALWAYS biopsy any suspicious lesion

Table 19. FIGO Staging Classification and Treatment of Vulvar Cancer

Stage	Description	Treatment
0	Intraepithelial neoplasia (VIN), carcinoma in situ	Local excision/superficial vulvectomy Laser ablation Local immunotherapy (imiquimod)
I	Tumour confined to vulva	Radical local excision + groin node dissection if >1 mm invasion
IA	≤2 cm lesion, confined to vulva, perineum ± stromal invasion ≤1 mm, no LN involment	Sentinel node dissection acceptable if lesion <4 cm and no suspicious nodes on examination
IB	>2 mm lesion or stromal invasion >1 mm, no LNs, confined to vulva or perineum	
II	Tumour any size with adjacent extension to 1/3 lower urethra, 1/3 lower vagina or anus Negative inguino-femoral LNs	Individualized Radical surgical excision ± chemoradiation
III	II plus positive inguino-femoral LNs	Individualized
IIIA	1 LN met (≥5 mm) or 1-2 LN mets (<5 mm)	Chemoradiation ± radical surgical excision
IIIB	2 LNs (≥5 mm) or >3 LNs mets (<5 mm)	
IIIC	Positive LNs with extracapsular spread	
IV	Regional (2/3 upper urethra, 2/3 upper vagina) spread or distant spread	Palliative therapy Individualized
IVA	(i) Spread to upper urethra ± vaginal mucosa, bladder, rectal mucosa or fixed to pelvic bone (ii) Fixed or ulcerated inguino-femoral LN	Chemoradiation ± radical surgical excision
IVB	Distant mets including pelvic LN	

Prognosis

- depends on stage and particularly nodal involvement (single most important predictor followed by tumour size)
- lesions >4 cm associated with poorer prognosis
- toxicities of therapy common
 - surgical site infection
 - lymphedema
 - radiation fibrosis, cystitis, proctitis
- overall 5-year survival rate: 79%

Vagina

BENIGN VAGINAL LESIONS

- **inclusion cysts**
 - cysts form at site of abnormal healing of laceration (e.g. episiotomy)
 - no treatment required
- **endometriosis**
 - dark lesions that tend to bleed at time of menses
 - treatment is excision
- **Gartner's duct cysts**
 - remnants of Wolffian duct, seen along side of cervix
 - treatment conservative unless symptomatic
- **urethral diverticulum**
 - can lead to recurrent urethral infection, dyspareunia
 - surgical correction if symptomatic

MALIGNANT VAGINAL LESIONS**Risk Factors**

- associated with HPV infection (analogous to cervical cancer)
- increased incidence in patients with prior history of cervical and vulvar cancer

Investigations

- cytology
 - significant false negative rate for existing malignancy (i.e. if gross lesion present, biopsy!)
- colposcopy
- Schiller test (normal squamous epithelium takes up Lugol's iodine)
- biopsy, partial vaginectomy (wide local excision for diagnosis)
- rule out disease on cervix, vulva, or anus (most vaginal cancers are actually metastatic from one of these sites)
- staging (see Table 20)

VAIN (Vaginal Intra-Epithelial Neoplasia)

- grades: analogous to cervical dysplasia
- treatment
 - must rule out invasive cancer via biopsies and colposcopy prior to conservative treatment
 - laser ablation vs. surgical excision vs. local immunotherapy (e.g. imiquimod)

Squamous Cell Carcinoma (SCC)

- 80-90% of vaginal cancer
- 2% of gynecological malignancies
- most common site is upper 1/3 of posterior wall of vagina
- 5-year survival – 42%
- clinical features
 - asymptomatic
 - painless discharge and bleeding
 - vaginal discharge (often foul-smelling)
 - vaginal bleeding especially during/post-coitus
 - urinary and/or rectal symptoms 2° to compression
- treatment
 - usually concurrent chemoradiation therapy for 1° vaginal cancer
 - consider radical hysterectomy/upper vaginectomy if early stage lesion and young patient

Adenocarcinoma

- most are metastatic, usually from the cervix, endometrium, ovary, or colon
- most primaries are clear cell adenocarcinomas
- 2 types: non-DES and DES syndrome
- management as for SCC

Diethylstilbestrol (DES) Syndrome

- fetal exposure to DES (due to maternal use) predisposes to cervical or vaginal clear cell carcinoma, occurs in 30-95% of exposed females
- if exposed, <1 in 1,000 risk of developing clear cell adenocarcinoma
- clinical features
 - adenosis is persistent Müllerian type glandular epithelium in vagina
 - DES exposure associated with malformations of upper vagina, cervix, and interior of uterus (T-shaped); cockscomb or hooded cervix, cervical collar, and pseudopolyps of cervix
- patients with DES exposure should have annual Pap tests (cervix and vagina) and digital vaginal exam for subepithelial masses
 - if any abnormality, refer for colposcopy

Table 20. FIGO Staging Classification of Vaginal Cancer (Clinical Staging)

Stage	Description
0	Intraepithelial neoplasia (VAIN), carcinoma in situ
I	Limited to the vaginal wall
II	Involves subvaginal tissue, NO pelvic wall extension
III	Pelvic wall extension
IV	Extension beyond true pelvis OR bladder/rectum involvement
IVA	Bladder ± rectal mucosal spread ± extension beyond true pelvis
IVB	Spread to distant organs



Prognosis
5 Year Survival Rates
 Stage I 70%
 Stage II 40%
 Stage III 30%
 Stage IV 15-20%

Fallopian Tube

- least common site for carcinoma of female reproductive system (0.3%)
- usually adenocarcinoma
- analogous to ovarian cancer (may be implicated in pathogenesis of ovarian cancer)
- more common in fifth and sixth decade

Clinical Features

- classic triad present in minority of cases, but very specific
 - watery discharge (most specific) = “hydrops tubae profluens”
 - vaginal bleeding or discharge in 50% of patients
 - crampy lower abdominal/pelvic pain
- most patients present with a pelvic mass (see *Ovarian Cancer*, GY38 for guidelines regarding diagnosis/investigation)

Treatment

- as for malignant ovarian tumours



Classic Triad (<15% of patients)
 1. Watery vaginal discharge
 2. Pelvic pain
 3. Vaginal bleeding



Current hypotheses suggest epithelial serous ovarian cancer originates from malignant fallopian tube cells.



With development of hypertension early in pregnancy (i.e. <20 weeks), think gestational trophoblastic disease!

Gestational Trophoblastic Disease/Neoplasia (GTD/GTN)

- refers to a spectrum of proliferative abnormalities of the trophoblast

Epidemiology

- 1/1000 pregnancies
- marked geographic variation – as high as 1/125 in Taiwan
- 80% benign, 15% locally invasive, 5% metastatic
- cure rate >95%

HYDATIDIFORM MOLE (Benign GTD)

- **complete mole**
 - most common type of hydatidiform mole
 - diffuse trophoblastic hyperplasia, hydropic swelling of chorionic villi, no fetal tissues or membranes present
 - 46XX or 46XY, chromosomes completely of paternal origin (90%)
 - 2 sperm fertilize empty egg or 1 sperm with reduplication
 - 15-20% risk of progression to malignant sequelae
 - risk factors
 - ♦ geographic (South East Asia most common)
 - ♦ others (maternal age >40 years, β -carotene deficiency, vitamin A deficiency) – not proven
 - clinical features
 - ♦ often present during apparent pregnancy with abnormal symptoms/findings:
 - vaginal bleeding (97%)
 - excessive uterine size for LMP (51%)
 - theca-lutein cysts >6 cm (50%)
 - pre-eclampsia (27%)
 - hyperemesis gravidarum (26%)
 - hyperthyroidism (7%)
 - beta-hCG >100,000 mIU/mL
 - no fetal heart detected
- **partial (or incomplete) mole**
 - hydropic villi and focal trophoblastic hyperplasia are associated with fetus or fetal parts
 - often triploid (XXY, XYY, XXX) with chromosome complement from both parents
 - ♦ usually related to single ovum fertilized by two sperm
 - low risk of progression to malignant sequelae (<4%)
 - associated with fetus, which may be growth-restricted and/or have multiple congenital malformations
 - clinical features
 - ♦ typically present similar to threatened/spontaneous/missed abortion
 - ♦ pathological diagnosis often made after D&C

Investigations

- quantitative beta-hCG levels (tumour marker) abnormally high for gestational age
- U/S findings:
 - if complete: no fetus (classic “snow storm” due to swelling of villi)
 - if partial: molar degeneration of placenta \pm fetal anomalies, multiple echogenic regions corresponding to hydropic villi, and focal intrauterine hemorrhage
- CXR (may show metastatic lesions)
- features of molar pregnancies at high risk of developing persistent GTN post-evacuation
 - local uterine invasion as high as 31%
 - beta-hCG >100,000
 - excessive uterine size
 - prominent theca-lutein cysts

Treatment

- suction D&C with sharp curettage and oxytocin
- Rhogam® if Rh negative
- consider hysterectomy (if patient no longer desires fertility)
- prophylactic chemotherapy of no proven benefit
- chemotherapy for GTN if develops after evacuation

Follow-up

- contraception required to avoid pregnancy during entire follow-up period
- serial beta-hCGs (as tumour marker) every week until negative x 3 (usually takes several weeks), then monthly for 6-12 months – prior to trying to conceive again
- increase or plateau of beta-hCG indicates GTN → patient needs chemotherapy

GTN (MALIGNANT GTD)

- **invasive mole or persistent GTN**
 - diagnosis made by rising or plateau in beta-hCG, development of metastases following treatment of documented molar pregnancy (see sidebar)
 - histology: molar tissue from D&C
 - metastases are rare (4%)
- **choriocarcinoma**
 - often present with symptoms from metastases
 - highly anaplastic, highly vascular
 - no chorionic villi, elements of syncytiotrophoblast and cytotrophoblast
 - may follow molar pregnancy, abortion, ectopic, or normal pregnancy
- **placental-site trophoblastic tumour**
 - rare aggressive form of GTN
 - abnormal growth of intermediate trophoblastic cells
 - low beta-hCG, production of human placental lactogen (hPL), relatively insensitive to chemotherapy

**GTN Diagnosis**

1. 4 values of persistently elevated beta-hCG plateau (days 1, 7, 14 and 21) or sequential rise of beta-hCG for 2 weeks (days 1, 7, 14) or longer
2. Lung metastases on CXR (rare)

CLASSIFICATION of GTN

- **non-metastatic**
 - ~15% of patients after molar evacuation
 - may present with abnormal bleeding
 - all have rising or plateau of beta-hCG
 - negative metastases on staging investigations
- **metastatic**
 - 4% patients after treatment of complete molar pregnancy
 - metastasis more common with choriocarcinoma which tends toward early vascular invasion and widespread dissemination
 - if signs or symptoms suggest hematogenous spread, don't biopsy (they bleed)
 - ♦ lungs (80%): cough, hemoptysis, CXR lesion(s)
 - ♦ vagina (30%): vaginal bleeding, "blue lesions" on speculum exam
 - ♦ pelvis (20%): rectal bleeding (if invades bowel), U/S lesion(s)
 - ♦ liver (10%): elevated LFTs, U/S or CT findings
 - ♦ brain (10%): headaches, dizziness, seizure (symptoms of space-occupying lesion), CT/MRI findings
 - highly vascular tumour → bleeding → anemia
 - all have rising or plateau of beta-hCG
 - classification of metastatic GTN
 - ♦ divided into good prognosis and bad prognosis
 - ♦ features of bad prognosis
 - long duration (>4 months from antecedent pregnancy)
 - high pre-treatment beta-hCG titre: >100,000 IU/24h urine or >40,000 mIU/mL of blood
 - brain or liver metastases
 - prior chemotherapy
 - metastatic disease following term pregnancy
 - ♦ good prognosis characterized by the absence of each of these features



Lungs are #1 site for malignant GTN metastases. When pelvic exam and chest x-ray are negative, metastases are uncommon.

Investigations – For Staging

- history and physical
- bloodwork: CBC, electrolytes, creatinine, beta-hCG, TSH, LFTs
- imaging: CXR, U/S pelvis, CT abdo/pelvis, CT brain
- if suspect brain metastasis but CT brain negative, consider lumbar puncture for CSF beta-hCG
 - ratio of plasma beta-hCG:CSF beta-hCG <60 indicates metastases

Table 21. FIGO Staging and Management of Malignant GTN

Stage	Findings	Management
I	Disease confined to uterine corpus	Single agent chemotherapy for low risk disease (WHO score ≤6) 1st line: pulsed – actinomycin D (Act-D) IV q2 wks Alternatives: MTX-based regimen 20% of patients need to switch to alternate single-agent regimen Combination chemotherapy (EMA-CO: etoposide, MTX, ACT-D, cyclophosphamide, vincristine) if high risk (WHO score ≥7) or if resistant to single agent chemotherapy Can consider hysterectomy if fertility not desired or placental-site trophoblastic tumour
II	Metastatic disease to genital structures	As above
III	Metastatic disease to lungs with or without genital tract involvement	As above
IV	Distant metastatic sites including brain, liver, kidney, GI tract	Usually high risk (EMA-CO) with surgical resection of sites of disease Persistence/resistance to chemotherapy Consider radiation for brain mets

Follow-up (for GTN)

- contraception for all stages to avoid pregnancy during entire follow-up period
- stage I, II, III
 - weekly beta-hCG until 3 consecutive normal results
 - then monthly x 12 months
- stage IV
 - weekly beta-hCG until 3 consecutive normal results
 - then monthly x 24 months

Treatment

- chemotherapy for all stages (see Table 21)

Common Medications

Table 22. Common Medications

Drug Name (Brand Name)	Action	Dosing Schedule	Indications	Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)
acyclovir (Zovirax®)	Antiviral; inhibits DNA synthesis and viral replication	First Episode: 400 mg PO tid x 7-10d Recurrence: 400 mg PO tid x 5d	Genital herpes	S/E: headache, GI upset D/I: zidovudine, probenecid
bromocriptine (Parlodel®)	Dopaminomimetic Agonist at D ₂ R Antagonist at D ₁ R Acts directly on anterior pituitary cells to inhibit synthesis and release of prolactin	Initial: 1.25-2.5 mg qhs with food Then: 2.5 mg bid with meals	Galactorrhea + amenorrhea 2° to hyperprolactinemia Prolactin-dependent menstrual disorders and infertility Prolactin-secreting adenomas (microadenomas, prior to surgery of macroadenomas)	S/E: nausea, vomiting, headache, postural hypotension, somnolence C/I: uncontrolled hypertension, pregnancy-induced hypertension, CAD D/I: domperidone, macrolides, octreotide
clomiphene citrate (Clomid®)	Increases output of pituitary gonadotropins which induces ovulation	50 mg daily x 5 days Try 100 mg daily if ineffective 3 courses = adequate trial	Patients with persistent ovulatory dysfunction (e.g. amenorrhea, PCOS) who desire pregnancy	S/E: Common – hot flashes, abdominal discomfort, exaggerated cyclic ovarian enlargement, accentuation of Mittelschmerz Rare – ovarian hyperstimulation syndrome, multiple pregnancy, visual blurring, birth defects C/I: pregnancy, liver disease, hormone-dependent tumours, ovarian cyst, undiagnosed vaginal bleeding
clotrimazole (Canesten®)	Antifungal; disrupt fungal cell membrane	Tablet: 100 mg/d intravaginally x 7d or 500 mg x 1 dose Cream (1 or 2%): 1 applicator intravaginally qhs x 3-7d Topical: apply bid x 7d	Vulvovaginal candidiasis	S/E: vulvar/vaginal burning
danazol (Cyclomen® – CAN) (Danocrine® – US)	Synthetic steroid that inhibits pituitary gonadotropin output and ovarian steroid synthesis Has mild androgenic properties	200-800 mg in 2-3 divided doses Used for 3-6 months Biannual hepatic U/S required if >6 month use	Endometriosis 1° menorrhagia/DUB	S/E: weight gain, acne, mild hirsutism, hepatic dysfunction C/I: pregnancy, undiagnosed vaginal bleeding, breastfeeding, severely impaired renal/hepatic/cardiac function, porphyria, genital neoplasia D/I: warfarin, carbamazepine, cyclosporine, tacrolimus, anti-hypertensives
doxycycline	Tetracycline derivative; inhibit protein synthesis	100 mg PO bid x ≥7d	Chlamydia, gonococcal infection, syphilis	S/E: GI upset, hepatotoxicity C/I: pregnancy, severe hepatic dysfunction D/I: warfarin, digoxin
fluconazole (Diflucan®)	Antifungal; disrupt fungal cell membrane	150 mg PO x 1 dose	Vulvovaginal candidiasis unresponsive to clotrimazole	S/E: headache, rash, nausea, vomiting, abdo pain, diarrhea D/I: terfenadine, cisapride, astemizole, hydrochlorothiazide, phenytoin, warfarin, rifampin
leuprolide (Lupron®)	Synthetic GnRH analog Induces reversible hypoestrogenic state	3.75 mg IM q1month or 11.25 mg IM q3months Usually ≤6 months, check bone density if >6 months	Endometriosis Leiomyomata DUB Precocious puberty	S/E: hot flashes, sweats, headache, vaginitis, reduction in bone density C/I: pregnancy, undiagnosed vaginal bleeding, breastfeeding
menotropin (Pergonal®)	Human Gonadotropin with FSH and LH effects; induce ovulation and stimulate ovarian follicle development	75-150 U of FSH and LH IM qd x 7-12d, then 10,000 U hCG one day after last dose	Infertility	S/E: bloating, irritation at injection site, abdo/pelvic pain, headache, nausea and vomiting C/I: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy
metronidazole (Flagyl®)	Bactericidal; forms toxic metabolites which damage bacterial DNA	2 g PO x 1 dose or 500 mg PO bid x 7d	Bacterial vaginosis, trichomonas vaginitis	S/E: headache, dizziness, nausea, vomiting, diarrhea, disulfiram-like reaction (flushing, tachycardia, nausea and vomiting) C/I: pregnancy (1 st trimester) D/I: cisapride, warfarin, cimetidine, lithium, alcohol

Table 22. Common Medications (continued)

Drug Name (Brand Name)	Action	Dosing Schedule	Indications	Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)
oxybutinin (Ditropan®)	Anticholinergic – relaxes bladder smooth muscle, inhibits involuntary detrusor contraction	5 mg PO bid-tid	Overactive bladder (urge incontinence)	S/E: dry mouth/eyes, constipation, palpitations, urinary retention C/I: glaucoma, GI ileus, severe colitis, obstructive uropathy, use with caution if impaired hepatic/renal function
tolterodine (Detrol®)	Anticholinergic	1-2 mg PO bid	Overactive bladder (urge incontinence)	S/E: anaphylaxis, psychosis, tachycardia, dry mouth/eyes, headache, constipation, urinary retention, chest pain C/I: glaucoma, gastric/urinary retention, use with caution if impaired hepatic/renal function
tranexamic acid (Cyklokapron®)	Anti-fibrinolytic, reversibly inhibits plasminogen activation	1-1.5 g tid-qid for first 4 days of cycle Ophthalmic check if used for several weeks	Menorrhagia	S/E: nausea, vomiting, diarrhea, dizziness, rare cases of thrombosis C/I: thromboembolic disease, acquired disturbances of colour vision, subarachnoid hemorrhage, age <15 yrs
urofolitropin (Metrodin®)	FSH	75 U/d SC x 7-12 d	Ovulation induction in PCOS	S/E: ovarian enlargement or cysts, edema and pain at injection site, arterial thromboembolism, fever, abdo pain C/I: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy
combined oral contraceptive pill (OCP)	Ovulatory suppression by inhibiting LH and FSH Decidualization of endometrium Thickening of cervical mucus to prevent sperm penetration		Contraception Disorders of menstruation	S/E: Estrogen-related – nausea, breast changes (tenderness, enlargement), fluid retention/bloating/edema, weight gain, migraines, thromboembolic events, liver adenoma, intermenstrual bleeding Progestin-related – amenorrhea/intermenstrual bleeding, headaches, breast tenderness, increased appetite, decreased libido, mood changes, hypertension, acne/oily skin, hirsutism D/I: rifampin, phenobarbital, phenytoin, primidone C/I: Absolute – known/suspected pregnancy, undiagnosed abnormal vaginal bleeding, prior thromboembolic events, thromboembolic disorder, active thrombophlebitis, cerebrovascular or coronary artery disease, estrogen-dependent tumours, impaired liver function associated with acute liver disease, congenital hypertriglyceridemia, smoker age >35 years, migraines with focal neurological symptoms (excluding aura), uncontrolled hypertension Relative – non focal migraines with aura <1 hour, diabetes mellitus complicated by vascular disease, SLE, controlled hypertension, hyperlipidemia, sickle cell anemia, gallbladder disease
intrauterine device (IUD) copper IUD (Nova-T®) progesterone-releasing IUD (Mirena®)	Copper IUD: mild foreign body reaction in endometrium which is toxic to sperm and alters sperm motility Progesterone-releasing IUD: decidualization of endometrium and thickening of cervical mucus, may suppress ovulation	Contraceptive effects last five years	Same as above	S/E: intermenstrual bleeding, bloating, headache (Mirena®), increased blood loss, duration of menses and dysmenorrhea (copper IUD only), expulsion (5% in the first year, greatest in first month), uterine wall perforation (1/5000), greater risk of ectopic pregnancy if pregnancy occurs, increased risk of PID within first 10 days of insertion only C/I: Absolute – known or suspected pregnancy, undiagnosed genital tract bleeding, acute or chronic PID, lifestyle risk for STIs, known allergy to copper or Wilson's Disease (copper IUD only) Relative – valvular heart disease, past history of PID or ectopic pregnancy, abnormalities of uterine cavity, intracavitary fibroids, severe dysmenorrhea or menorrhagia (copper IUD only), cervical stenosis, immunosuppressed individuals

References

Books/Manuals

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, Text Revision. Washington, DC. American Psychiatric Publishing Inc., 2000.

Dickey R. Managing Contraceptive Pill Patients 9th edition. EMIS Inc. Medical Publishers., USA 1998.

Cunningham FG, McDonald PC, and Gant NF (eds.), Williams Obstetrics, 14th ed, Appleton and Lange, 1993.

Hacker NF and Moore JG (eds), Essentials of Obstetrics and Gynecology. 2nd ed. N.F. Hacker and J.G. Moore (eds). W.B. Saunders Co., 1992.

Guidelines

ACOG Practice Bulletin – Clinical Management Guidelines for Obstetrician-Gynecologists. Premenstrual Syndrome. Number 15, April 2000.

Davis V and Dunn S. Emergency Postcoital Contraception. SOGC Clinical Practice Guidelines. No. 82 July 2000.

National guideline for the treatment of bacterial vaginosis. Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases). Sex Transm Infect. 1999; 75 Suppl 1: S1 6-8.

Ontario Cervical Screening Practice Guidelines. June 2005. <http://www.cancercare.on.ca/index – cervical screening.htm>

Paley PJ. Screening for the major malignancies affecting women: current guidelines. Am J Obstet Gynecol 2001;184(5): 1021-30.

Public Health Agency of Canada, 2008. Updates on Canadian guidelines on Sexually Transmitted Infections 2006 Edition. <http://www.phac-aspc.gc.ca/std-mts/sti-its/guide-lignesdir-eng.php>.

SOGC News Release. New recommendations from national ob/gyn society address Depo-Provera, bone loss. May 2006. http://www.sogc.org/media/pdf/advisories/dmpa-may2006_e.pdf.

Journal Articles

Anderson, GL, Limacher, M, et al. (WHI Steering Committee). Effects of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy – The Women's Health Initiative Randomized Controlled Trial. JAMA 2004; 291(14): 1701-1712.

Bélisle S, Blake J, Basson R, Deslandes S, Graves G, Grigoriadis S, et al. Canadian Consensus Conference on Menopause, 2006 update. J Obstet Gynaecol Can 2006;28(2 Suppl 1):S1-S94.

Canadian Consensus Conference on Menopause, 2006 Update. JOGC 2006;171.

Creanga AA, Bradley HM, McCormick C, Witkop CT. Use of metformin in polycystic ovary syndrome: a meta-analysis. Obstet Gynecol 2008;111(4):959-68.

Davey E, Barratt A, Irwig L et al. Effect of study design and quality of unsatisfactory rates, cytology classifications, and accuracy in liquid-based versus conventional cervical cytology: a systematic review. Lancet 2006; 367: 122-32.

Erdman JN. Human Rights in Health Equity: Cervical cancer and Hpv vaccines. American journal of law & medicine 2009; 35: 365-387.

Espeland, MA, Rapp SR, Shumaker SA, et al. Conjugated Equine Estrogens and Global Cognitive Function in Postmenopausal Women – Women's Health Initiative Memory Study. JAMA 2004; 291(24): 2959-2968.

Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605-613.

Lipscomb GH, McCord ML, Stovall TG et al. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. NEJM 2001; 341: 1974-1978.

Luciano AA, Solima RG. Ectopic Pregnancy: From Surgical Emergency to Medical Management. Ann NY Acad Sci 2001; 943: 235-254.

Manson JE, Martin KA. Postmenopausal hormone replacement therapy. NEJM 2001;345(1):34-40.

Moore RG, Jabre-Raughley M, Brown AK, Robison KM, Miller MC, Allard WJ, Kurman RJ, Bast RC, Skates SJ. Comparison of a novel multiple marker assay vs. the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. Am J Obstet Gynecol. May 2010. In press. Corrected proof

Lujan ME, Chizen DR, Pierson RA. Diagnostic criteria for polycystic ovary syndrome: Pitfalls and controversies. J Obstet Gynaecol Can. 2008.

Marchbanks PA, Aneger JF, Coulman CB, et al. Risk factors for ectopic pregnancy: a population based study. JAMA 1998; 259: 1823-1827.

Martin JL, Williams KS, Abrams KR, et al. Systematic review and evaluation of methods of assessing urinary incontinence. Health Technol Assess 2006;10(6):1-132, iii-iv.

Rambout L, Hopkins L, Fung Kee Fung M, et al. Prophylactic vaccination against human papillomavirus infection in women: a systematic review of randomized controlled trials. CMAJ 2007;177.

Ratner S and Ofri D. Menopause and hormone replacement therapy. West J Med 2001;175:32-34.

Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, Walker AM. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. Obstet Gynecol 2007;110(3):587-93.

Shapter AP. Gestational trophoblastic disease. Obs Gynecol Clin North Am 2001; 28(4): 805-17.

Shumaker SA, Legault C, Kuller L, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women – Women's Health Initiative Memory Study. JAMA 2004; 291(24): 2947-2958.

Tingulstad S, Hagen B, Skjeldestad FE, et al. The risk of malignancy index to evaluate potential ovarian cancers in local hospitals. BR J Obstet Gynecol. 1999;93(3):448-52.

Wooltorton, E. The Evra (ethinyl estradiol/norelgestromin) Contraceptive patch: estrogen exposure concerns. CMAJ 2006; 174(2): 164-165.

Wooltorton E. Medroxyprogesterone acetate (Depo-Provera) and bone mineral density loss. JAMA 2005; 172 (6): 746.

Women's Health Coordinating Council. Clinician Information Sheet: HPV Vaccine for Cervical Cancer Prevention. Massachusetts General Hospital. August 21, 2006.

Websites

Management of Uterine Fibroids. Summary, Evidence Report/Technology Assessment: Number 34. AHRQ Publication No. 01-E051, January 2001.

Agency for Healthcare Research and Quality, Rockville, MD. <http://www.ahrq.gov/clinic/utsumm.htm>

Sexuality and U. Society of Obstetricians and Gynaecologists of Canada. <http://www.sexualityandu.ca>

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Immune Thrombocytopenic Purpura (ITP)			
Heparin-Induced Thrombocytopenia (HIT)			
Thrombotic Thrombocytopenic Purpura (TTP)			
and Hemolytic Uremic Syndrome (HUS)			
Von Willebrand's Disease (vWD)			



Basics of Hematology



Erythrocyte – carries oxygen from lungs to peripheral tissues

Reticulocyte – immature erythrocyte

Neutrophil – granulocyte integral in innate immunity; main cell in acute inflammation

Eosinophil – involved in response to parasites (especially helminths) and allergic response

Basophil – granulocyte mainly involved in allergy and parasitic infection

Lymphocyte – integral cell in adaptive immunity

Monocyte – involved in innate immunity; can differentiate into macrophage or dendritic cell

Platelet – mediator of primary hemostasis

Plasma – liquid component of blood containing water, proteins, coagulation factors and immunoglobulins

Serum – equivalent to plasma minus clotting factors and fibrinogen

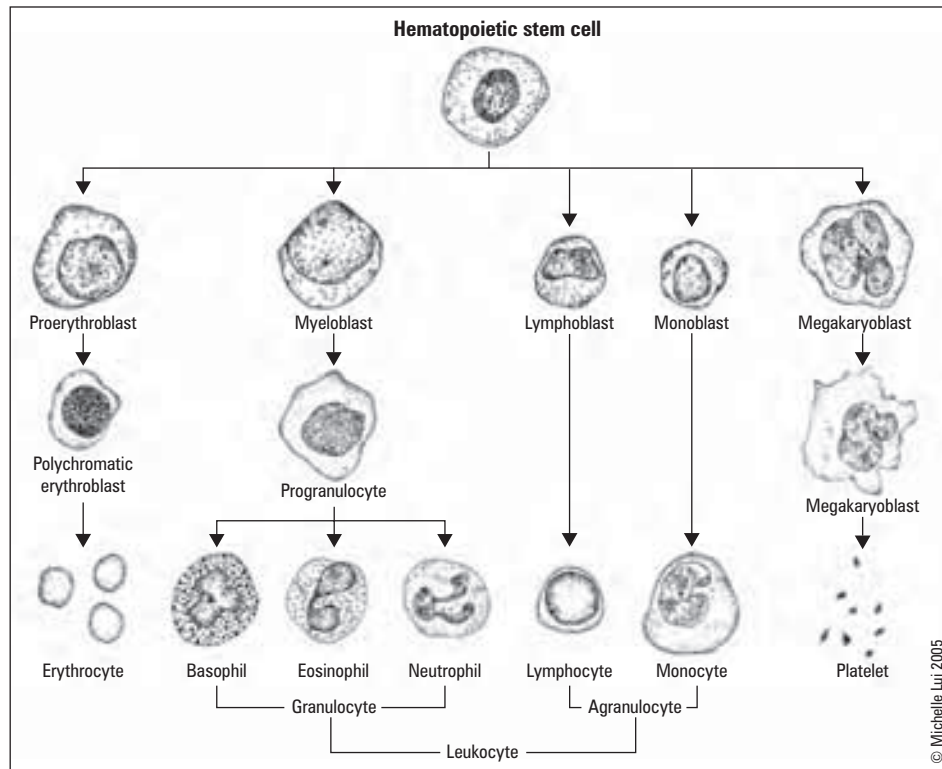


Figure 1. Hematopoiesis

- over 10^{11} blood cells are produced daily
- sites of hematopoiesis in adults: pelvis, sternum, vertebral bodies
- lifespan of mature blood cells
 - erythrocytes (120 days); neutrophils (~1 day); platelets (10 days); lymphocytes (varies – memory cells persist for years)
- role of lymphoid organs
 - spleen: part of reticuloendothelial system; removes aged RBCs, removes antibody-coated bacteria/cells, site of antibody production
 - thymus: site of T-cell maturation, involutes with age
 - lymph nodes: sites of B and T cell activation (adaptive immune response)

Complete Blood Count

Table 1. Common Terms Found on CBC

Test	Definition	Normal Values*
Red blood cell (RBC) count	The number of RBCs per volume of blood	$4.2-6.9 \times 10^9/\text{mm}^3$
Hemoglobin (Hb)	Amount of oxygen-carrying protein in the blood	130-180 g/L (13-18 g/dL) (male) 120-160 g/L (12-16 g/dL) (female)
Hematocrit (Hct)	Percentage of a given volume of whole blood occupied by packed RBCs	45%-62% (male) 37%-48% (female)
Mean corpuscular volume (MCV)	Measurement of size of RBCs	$80-100 \mu\text{m}^3$
Mean corpuscular Hb (MCH)	Amount of oxygen-carrying Hb inside RBCs	27-32 pg/cell
Mean corpuscular Hb concentration (MCHC)	Average concentration of Hb inside RBCs	32%-36%
RBC distribution width (RDW)	Measurement of variance in RBC size	11.0%-15.0%
White blood cell (WBC) count	The number of WBCs per volume of blood	$4.3-10.8 \times 10^9/\text{mm}^3$
WBC differential	Includes neutrophils, eosinophils, basophils, lymphocytes and monocytes	
Platelet count	The number of platelets per volume of blood	$150-400 \times 10^9/\text{mm}^3$
Mean platelet volume (MPV)	Measurement of platelet size	
Reticulocytes	Immature RBCs that contain no nucleus but have residual RNA	Normally make up 1% of total RBC count

*Normal values may vary depending on site



Clinical Use of RDW

To distinguish the etiologies of microcytosis:
Fe deficiency – increased RDW (anisocytosis)
Thalassemia minor – normal RDW



Absolute Neutrophil Count (ANC) =
WBC count \times (%PMNs + %bands)
Beware of fever + ANC $<0.5 \times 10^9/\text{L}$ =
FEBRILE NEUTROPENIA

Approach for Interpreting CBC

- consider values in the context of individual's baseline
 - up to 5% of population without disease may have values outside "normal" range
 - an individual may display a substantial change from their baseline without violating "normal" reference range
- is one cell line affected or are several?
 - if all lines are low: consider pancytopenia (see *Pancytopenia*, H7)
 - if RBCs and platelets are low: consider microangiopathic hemolytic anemia (MAHA) (see H21)
 - if single cell line affected: see corresponding section in *Common Presenting Problems*, H5

Blood Film Interpretation

RED BLOOD CELLS

Size

- microcytic (MCV<80), normocytic (MCV=80-100), macrocytic (MCV>100)
- anisocytosis: RBCs with increased variability in size (increased RDW)
 - iron deficiency anemia, thalassemia major, myelofibrosis

Colour

- hypochromic: increase in size of central pallor (normal = less than 1/3 of RBC diameter)
 - iron deficiency anemia, anemia of chronic disease, hemolytic anemias, sideroblastic anemia
- polychromasia: increased reticulocytes (pinkish-blue cells)
 - increased RBC production by the marrow

Shape (see Table 2 and Figure 2)

- poikilocytosis: increased proportion of RBCs of abnormal shape
 - iron deficiency anemia, myelofibrosis

Table 2. Common Erythrocyte Shapes

Shape	Definition	Associated Conditions
Discocyte	Biconcave disc	Normal RBC
Spherocyte	Spherical RBC (due to loss of membrane)	Hereditary spherocytosis, immune hemolytic anemia
Elliptocyte/Ovalocytes	Oval-shaped, elongated RBCs <ul style="list-style-type: none"> Elliptocytes: the RBC long axis is $\geq 2\times$ the length of the short axis Ovalocytes: the RBC long axis is $< 2\times$ the length of the short axis 	Hereditary elliptocytosis, megaloblastic anemia, myelofibrosis, iron-deficiency, MDS
Schistocytes (helmet cells)	Fragmented cells (due to traumatic disruption of membrane)	Microangiopathic hemolytic anemia (HUS/TTP, DIC, pre-eclampsia, HELLP, malignant HTN), vasculitis, glomerulonephritis, prosthetic heart valve
Sickle cell	Sickle-shaped RBC (due to polymerization of hemoglobin S)	Sickle cell disorders: HbSC, HbSS
Codocyte (target cell)	"Bull's eye" on dried film	Liver disease, hemoglobin SC, thalassemia, Fe deficiency, asplenia
Dacrocyte (teardrop cell)	Single pointed end, looks like a teardrop	Myelofibrosis, thalassemia major, megaloblastic anemia
Acanthocyte (spur cell)	Distorted RBC with irregularly distributed thorn-like projections (due to abnormal membrane lipids)	Severe liver disease (spur cell anemia), starvation/anorexia, post-splenectomy
Echinocyte (burr cell)	RBC with numerous regularly spaced, small spiny projections	Uremia, HUS, burns, cardiopulmonary bypass, post-transfusion, storage artifact
Rouleaux formation	Aggregates of RBC resembling stacks of coins Due to increased plasma concentration of high molecular weight proteins	Pregnancy: most common cause; due to physiological increase in fibrinogen Inflammatory conditions: due to polyclonal immunoglobulins Plasma cell dyscrasias: due to monoclonal paraproteinemia, eg. multiple myeloma, macroglobulinemia Storage artifact

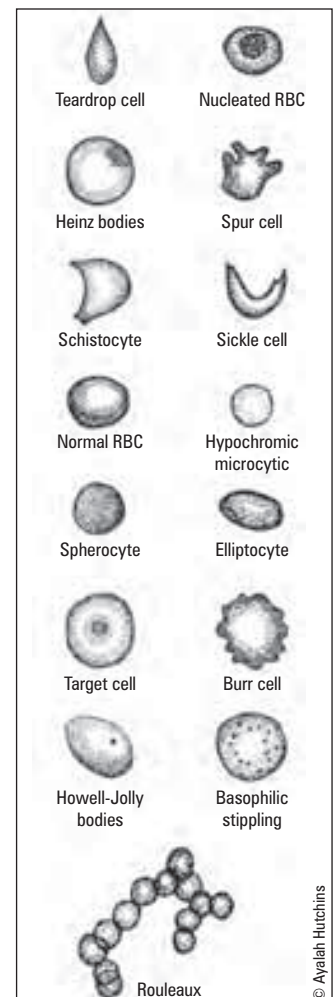


Figure 2. Morphology

Table 3. RBC Inclusions (see Figure 2)

Inclusions	Definition	Associated Conditions
Nucleus	Present in erythroblasts (immature RBCs)	Hyperplastic erythropoiesis (seen in hypoxia, hemolytic anemia), extramedullary hematopoiesis (in BM infiltration)
Heinz bodies	Denatured and precipitated hemoglobin	G6PD deficiency (post-exposure to oxidant), thalassemia, unstable hemoglobins
Howell-Jolly bodies	Small nuclear remnant resembling a pyknotic nucleus	Post-splenectomy, hyposplenism (sickle cell disease), neonates, megaloblastic anemia
Basophilic stippling	Deep blue granulations indicating ribosome aggregation	Thalassemia, heavy metal (Pb, Zn, Ag, Hg) poisoning, megaloblastic anemia, hereditary (pyrimidine 5'nucleotidase deficiency)
Sideroblasts	Erythrocytes with Fe containing granules in the cytoplasm	Hereditary, idiopathic, drugs, hypothyroidism (see <i>Sideroblastic Anemia</i> , H15)

WHITE BLOOD CELLS

- lymphocytes: comprise 30-40% of white cells
 - Reed-Sternberg cell: giant, multinucleated B-lymphocyte
 - ♦ seen in Hodgkin's lymphoma, other lymphoproliferative disorders, reactive nodes
 - smudge cells: lymphocytes damaged during preparation of the blood smear indicating cell fragility
 - ♦ seen in Chronic Lymphocytic Leukemia (CLL) and other lymphoproliferative disorders
- neutrophils
 - normally only mature neutrophils (with 2-4 lobed nucleus) and band neutrophils (immediate precursor with horseshoe-shaped nucleus) are found in circulation
 - hypersegmented neutrophil: >5 lobes suggests megaloblastic process (B₁₂ or folate deficiency)
 - left shift: increase in granulocyte precursors (bands, metamyelocytes, myelocytes, promyelocytes, blasts) in circulation
 - ♦ seen in acute infections, pregnancy, hypoxia, shock, CML
- blasts
 - immature, undifferentiated cells; associated with acute leukemia, MDS, severe infection
 - Auer rods: clumps of granular material that form long needles in the cytoplasm of myeloblasts
 - ♦ pathognomonic for Acute Myeloid Leukemia (AML)

PLATELETS

- small purple anuclear cell fragments

**Bone Marrow Aspiration and Biopsy**

- sites: posterior iliac crest, sternum, anterior iliac crest
- possible analyses
 - aspiration: histology, flow cytometry, cytogenetics, molecular studies, microbiology (C&S, AFB)
 - biopsy: for histology

Indications

- unexplained CBC abnormalities
- diagnosis and evaluation of plasma cell disorders and leukemias
- diagnosis and staging of lymphoma or solid tumours
- evaluate iron metabolism and stores
- evaluate suspected deposition and storage disease (e.g. amyloidosis, Gaucher's disease)
- evaluate fever of undetermined origin, suspected mycobacterial, fungal or parasitic infections, or granulomatous disease
- unexplained splenomegaly
- confirm normal bone marrow in potential allogenic hematopoietic cell donor

Contraindications

- absolute: hemophilia, severe DIC
- thrombocytopenia not a contraindication – may need platelet transfusion prior to procedure

Common Presenting Problems



Anemia

Definition

- a decrease in red blood cell (RBC) mass that can be detected by hemoglobin (Hb) concentration, hematocrit (Hct), and RBC count
 - adult males: Hb <135 g/L, (13.5 g/dL) or Hct <41%
 - adult females: Hb <120 g/L, (12 g/dL) or Hct <36%

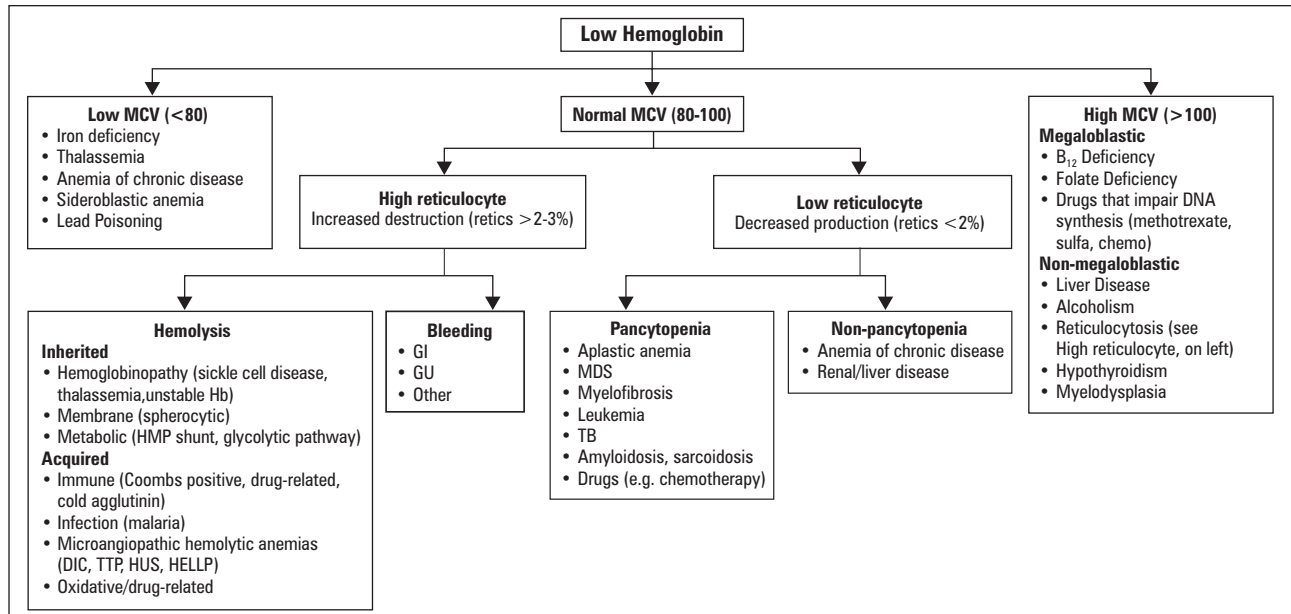


Figure 3. Approach to Anemia

Clinical Features

- history
 - symptoms of anemia: fatigue, malaise, weakness, dyspnea, decreased exercise tolerance, palpitations, headache, dizziness, tinnitus, syncope
 - acute vs. chronic, bleeding, systemic illness, diet, alcohol, family history
 - rule out pancytopenia (recurrent infection, mucosal bleeding/easy bruisability)
- physical signs
 - HEENT: pallor in mucous membranes and conjunctiva at Hb <90 g/L (<9 g/dL), ocular bruits at Hb <55 g/L (<5.5 g/dL)
 - cardiac: tachycardia, orthostatic hypotension, systolic flow murmur, wide pulse pressure, signs of CHF
 - dermatologic: pallor in palmar skin creases at Hb <75 g/L (<7.5 g/dL), jaundice (if due to hemolysis)

Investigations

- rule out dilutional anemia (low Hb due to increased effective circulating volume)
- CBC with differential (note MCV, RDW)
- reticulocyte count
- blood film
- rule out gastrointestinal disease in iron deficiency anemia
- additional laboratory investigations as indicated (see *Microcytic Anemia*, H12, *Normocytic Anemia*, H16, *Hemolytic Anemia*, H17 and *Macrocytic Anemia*, H22)



Reticulocytes

- Reticulocytes are immature erythrocytes and are markers of erythrocyte production
- Normally they should increase when there is a decrease in RBC
- With blood loss, reticulocytes should increase 2-3x initially and then 5-7x over the next week
- A normal reticulocyte count in anemia should be interpreted as a sign of decreased production

Polycythemia



Definition

- an increase in the number of RBCs: Hb >185 g/L or Hct >52% (males); Hb >165 or Hct >47% (females and African males)

Etiology

- relative/spurious erythrocytosis (decreased plasma volume): diuretics, severe dehydration, burns, “stress” (Gaisböck’s syndrome)
- absolute erythrocytosis
 - primary (low or normal erythropoietin)
 - ♦ polycythemia rubra vera (PRV) (see PRV, H38)
 - secondary (elevated erythropoietin)
 - ♦ poor tissue oxygenation/hypoxia
 - ♦ pulmonary disease: COPD, sleep apnea, pulmonary hypertension
 - ♦ cardiovascular disease: R → L shunt (Eisenmenger syndrome)
 - ♦ RBC defects (Hb with increased O₂ affinity, methemoglobinemia)
 - ♦ carbon monoxide poisoning (heavy smoking)
 - ♦ high altitude
 - inappropriate production of erythropoietin
 - ♦ renal cell carcinoma, cerebellar hemangioblastoma, hepatocellular carcinoma, uterine leiomyomas, ovarian tumour
 - ♦ other: polycystic kidney disease, post-kidney transplant, hydronephrosis, androgens

Clinical Features

- secondary to high red cell mass and hyperviscosity
 - headache, dizziness, tinnitus, visual disturbances
 - symptoms of angina, CHF
- thrombosis (venous or arterial) or bleeding (abnormal platelet function)
- physical findings
 - hepatomegaly, plethora (ruddy complexion) of face (70%) and/or palms

Investigations

- RBC mass: normal suggests relative erythrocytosis (confirms increased red cell production, rules out decreased plasma volume)
- serum erythropoietin (Epo): increased Epo suggests autonomous production or hypoxia and rules out PRV
 - search for tumour as source of Epo as indicated (e.g. abdominal U/S, CT head)
- arterial pO₂: decreased pO₂ suggests hypoxic etiology
- sleep studies if history suggestive of sleep apnea
- carboxyhemoglobin (hemoglobin-carbon monoxide complex) level, hemoglobin O₂ affinity

Treatments

- if secondary: treat underlying cause
 - O₂ for hypoxemia, CPAP for sleep apnea, surgery for EPO-secreting tumours
- phlebotomy



Must rule out factitious thrombocytopenia – platelet clumping (secondary to EDTA antibodies)



Thrombocytopenia

Definition

- platelet count $<150 \times 10^9/L$

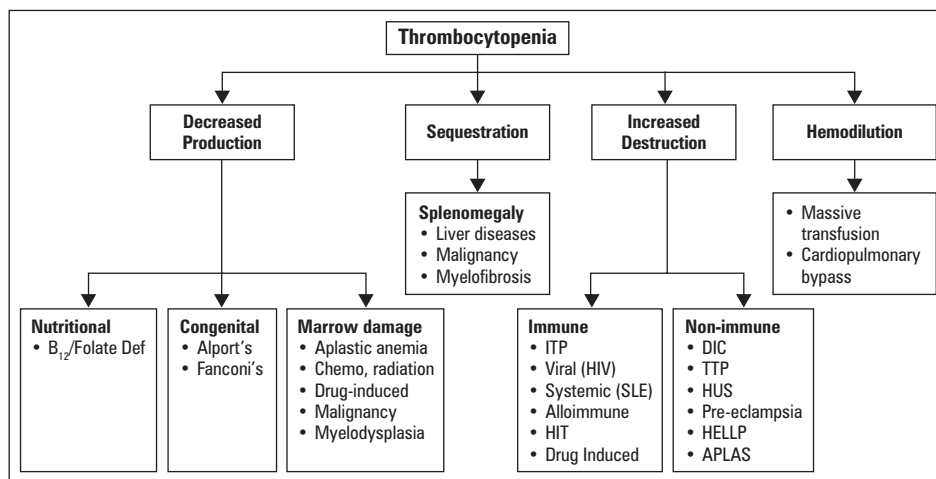


Figure 4. Approach to Thrombocytopenia

Adapted from Cecil's Essentials of Medicine

APLAS = Antiphospholipid Antibody Syndrome

Clinical Features

- history: bleeding gums, epistaxis, bleeding post-surgical procedures, metromenorrhagia
- physical exam: bruising, petechiae, ecchymoses, non-palpable purpura
 - hemarthrosis and deep muscle hematomas are rarely initial signs in patients with primary hemostatic disorders
- see *Disorders of Primary Hemostasis*, H26, for complications of thrombocytopenia

Investigations

- CBC and differential
- blood film
 - decreased production: possible other cell line abnormalities, blasts, hypersegmented PMNs, leukoerythroblastic changes
 - increased destruction: large platelets, schistocytes (seen in MAHA)
- work-up for nutritional deficiencies: vit B₁₂, RBC folate
- LFTs

Thrombocytosis

Definition

- platelet count $>500 \times 10^9/L$
- reactive thrombocytosis: acute phase reactant (e.g. surgery, inflammation, infection, trauma, bleeding, iron deficiency, neoplasms)
- autonomous thrombocytosis: due to myeloproliferative or myelodysplastic disorders [e.g. CML, primary myelofibrosis, polycythemia rubra vera (PRV), myelodysplastic syndrome (MDS)]

Clinical Features

- history: trauma, surgery, splenectomy, infection, inflammation, bleeding, iron deficiency, prior diagnosis of chronic hematologic disorder, constitutional symptoms indicating malignancy
- autonomous thrombocytosis more likely to cause vasomotor symptoms (headache, visual disturbances, lightheadedness, atypical chest pain, acral dysesthesia, erythromelalgia, livedo reticularis, aquagenic pruritus)
- clotting risk, bleeding risk (rare)
- physical exam: splenomegaly can be seen in myeloproliferative disorders

Investigations

- CBC, peripheral blood smear, serum ferritin concentration
- non-specific markers of infection or inflammation (e.g. CRP, ESR, plasma fibrinogen, ferritin)
- if reactive process has been ruled out, bone marrow biopsy may be required to determine cause of autonomous thrombocytosis

Pancytopenia

Definition

- a decrease in all hematopoietic cell lines

Clinical Features

- anemia – fatigue
- leukopenia – recurrent infections
- thrombocytopenia – mucosal bleeding and ecchymoses

Investigations

- CBC and differential, blood film
- investigate secondary causes: HIV test, serum B₁₂, RBC folate, ANA
- often requires bone marrow biopsy to determine cause

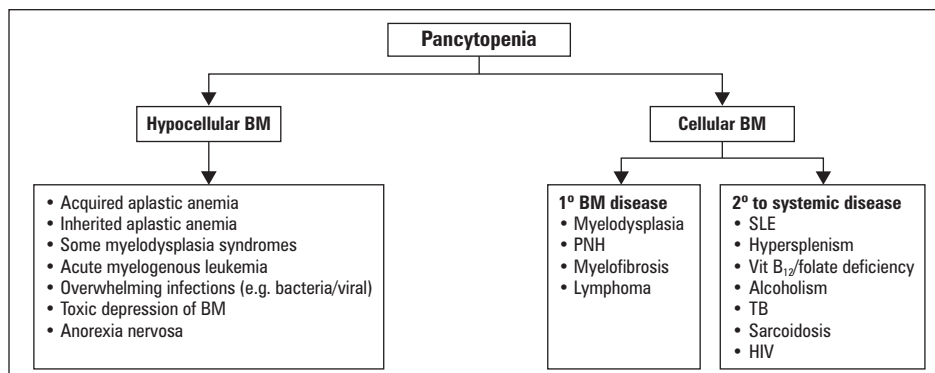


Figure 5. Approach to Pancytopenia

PNH = Paroxysmal Nocturnal Hemoglobinuria

Neutrophilia

Definition

- absolute neutrophil count (ANC) $>7.7 \times 10^9/L$

Etiology

- primary neutrophilia
 - hereditary neutrophilia (autosomal dominant)
 - chronic idiopathic neutrophilia in otherwise healthy patients
 - chronic myelogenous leukemia (CML)
 - other myeloproliferative disorders (PRV, ET, myelofibrosis)
 - leukocyte adhesion deficiency
- secondary neutrophilia
 - smoking – most common cause of mild neutrophilia
 - infection – leukocytosis with left shift \pm toxic granulation, Döhle bodies (intra-cytoplasmic structures composed of agglutinated ribosomes)
 - inflammation – e.g. RA, IBD, chronic hepatitis, MI, PE, burns
 - malignancy – hematologic (i.e. marrow invasion by tumour) and nonhematologic (especially large cell lung cancer)
 - stress/exercise/epinephrine – movement of neutrophils from marginated pool into circulating pool
 - medications – glucocorticoids, beta-agonists (e.g. epinephrine), lithium



Left Shift

Refers to an increase in granulocyte precursors in the peripheral smear (myelocytes, metamyelocytes, promyelocytes, blasts). If present, implies increased marrow production of granulocytes (e.g. inflammation, infection, G-CSF administration, CML).

The presence of predominantly blasts in the peripheral smear without cells between mature neutrophil and blast suggests clonal cell disorder (MDS, acute leukemias).

Clinical Features

- look for signs and symptoms of fever, inflammation, malignancy to determine appropriate further investigations
- examine oral cavity, teeth, peri-rectal area, genitals and skin for signs of infection

Investigations

- CBC differential: mature neutrophils or bands $>20\%$ of total WBC suggests infection/inflammation
- blood film: Döhle bodies, toxic granulation, cytoplasmic vacuoles in infection
- review other blood counts

Neutropenia

Definition

- mild:** ANC $1.0\text{--}1.5 \times 10^9/L$
- moderate:** ANC $0.5\text{--}1.0 \times 10^9/L$ (risk of infection starts to increase)
- severe:** ANC $<0.5 \times 10^9/L$

Etiology

- decreased production
 - hematological diseases – idiopathic, aplastic anemia, myelofibrosis, BM infiltration
 - infection – TB, typhoid, EBV, malaria, viral hepatitis, HIV
 - drug-induced – alkylating agents, antimetabolites, anticonvulsants, antipsychotics, anti-inflammatory agents, anti-thyroid drugs
 - toxic – high dose radiation, chemicals (e.g. benzene, DDT)
 - nutritional deficiency – B₁₂, folate
 - idiopathic – constitutional neutropenia, benign cyclic neutropenia
- peripheral destruction
 - antineutrophil antibodies
 - spleen or lung trapping
 - autoimmune disorders – RA, SLE
 - Wegener's granulomatosis
 - drugs – haptens (e.g. α -methyl dopa)
- excessive margination (transient neutropenia)
 - idiopathic (most common)
 - overwhelming bacterial infection
 - hemodialysis
 - racial variation (e.g. people of African descent commonly have mild neutropenia)

Clinical Features

- fever, chills (only if infection)
- infection by endogenous bacteria (e.g. *S. aureus*, gram negatives from GI and GU tract)
- painful ulceration on skin, anus, mouth and throat following colonization by opportunistic organisms
- avoid digital rectal exam

Investigations

- depends on degree of neutropenia and symptoms
- ranges from observation with frequent CBCs to bone marrow aspiration and biopsy

Treatment

- regular dental care – chronic gingivitis and recurrent stomatitis major sources of morbidity
- febrile neutropenia (see [Infectious Diseases](#), ID44)
- in severe immune-mediated neutropenia, G-CSF may increase neutrophil counts
 - if no response to G-CSF, then immunosuppression (e.g. steroids, cyclosporine, methotrexate)

Lymphocytosis

Definition

- absolute lymphocyte count $>4 \times 10^9/L$

Etiology

- infection
 - viral infections (majority)
 - TB, pertussis, brucellosis, toxoplasmosis
- physiologic response to stress (e.g. trauma, status epilepticus)
- hypersensitivity (e.g. drugs, serum sickness)
- autoimmune (e.g. rheumatoid arthritis)
- neoplasm (e.g. ALL, CLL, lymphoma)

Investigations/Treatment

- peripheral smear
 - smudge cells → do flow cytometry to rule out clonal process
 - atypical lymphocytes → suggestive of viral infection (EBV or others)
- treat underlying cause

Lymphocytopenia

Definition

- absolute lymphocyte count $<1.5 \times 10^9/L$

Etiology

- idiopathic CD4+ lymphocytopenia
- chemotherapeutic agents
- radiation
- HIV/AIDS, hepatitis B, hepatitis C, autoimmune disease (e.g. SLE)
- malignancy

Clinical Features

- opportunistic infections (see [Infectious Diseases](#))

Treatment

- treat underlying cause
- treat opportunistic infections aggressively and consider antimicrobial prophylaxis (see [Infectious Diseases](#), ID49)



G-CSF = Neupogen® = Filgrastim
GM-CSF = Leukine® = Sargramostim

Prophylactic Hematopoietic Colony-Stimulating Factors on Mortality and Infection

Ann Intern Med 2007; 147:400-11

Purpose: To review the effects of colony-stimulating factor (CSF) on mortality, infections, and febrile neutropenia in patients undergoing chemotherapy or stem-cell transplant (SCT).

Study Selection: 148 randomized control trials comparing the effects of CSFs to either placebo or no therapy were included. Prophylactic CSFs were given concurrently with or after initiation of chemotherapy.

Results: There were no differences in all-cause mortality or infection-related death between CSF and placebo groups. Compared to placebo or no therapy, CSFs reduced infection rate (median rate 38.9% vs. 43.1%; rate ratio 0.85), microbiologically documented infections (MR 23.5% vs. 28.6%; rate ratio 0.86), and febrile neutropenia (MR 25.3% vs. 44.2%; rate ratio 0.71).

Conclusions: Prophylactic CSFs decreases infection rates and episodes of febrile neutropenia in patients undergoing chemotherapy or SCT, but has no effect on mortality.

**Basophilia and/or Eosinophilia**

Can be an indicator of Chronic Myeloid Leukemia or other myeloproliferative disease, associated with pruritis due to excessive histamine production.

Eosinophilia

- absolute eosinophil count $>0.5 \times 10^9/L$
- most common causes are parasitic (usually helminth) infections and allergic reactions
- less common causes:
 - polyarteritis nodosa
 - cholesterol emboli
 - CML
 - Hodgkin's disease
 - adrenal insufficiency
- hypereosinophilic syndrome
 - 6 months of eosinophilia with no other detectable causes
 - can involve heart, bone marrow, CNS

Agranulocytosis

- severe depletion of granulocytes (neutrophils, eosinophils, basophils) from the blood and granulocyte precursors from bone marrow
- associated with drug use in 70% of cases: e.g. clozapine, thionamides (antithyroid drugs), sulfasalazine and ticlopidine
- pathogenesis
 - immune-mediated destruction of circulating granulocytes by drug-induced antibodies or direct toxic effects upon marrow granulocytic precursors
- abrupt onset of fever, chills and weakness, oropharyngeal ulcers
- high fatality without vigorous treatment

Investigations/Treatment

- discontinue offending drug
- pan-culture and screen for infection if patient is febrile (blood cultures x2, urine culture and chest x-ray as minimum, initiate broad-spectrum antibiotics)
- consider bone marrow aspirate and biopsy if cause unclear
- consider G-CSF (growth factor that stimulates neutrophil production)

Leukemoid Reactions

- blood findings resembling those seen in certain types of leukemia which reflect the response of healthy BM to cytokines released due to infection or trauma
- leukocytosis $>50 \times 10^9/L$, marked left shift (myelocytes, metamyelocytes, bands in peripheral blood smear)
- important to rule out CML
- differential diagnosis:
 - myeloid leukemia: pneumonia, other acute bacterial infections, intoxications, burns, malignant disease, severe hemorrhage or hemolysis
 - lymphoid leukemia: pertussis, TB, infectious mononucleosis
- monocytic leukemia: TB

Approach to Lymphadenopathy

Clinical Features

- history
 - constitutional/B-symptoms – weight loss, anorexia, fever, night sweats
 - ♦ seen in TB, lymphoma, other malignancies
 - symptoms of infection or malignancy
 - exposures – cats (cat scratch – *Bartonella henselae*), ticks (Lyme disease – *Borrelia burgdorferi*), high risk behaviors (HIV)
 - joint pain/swelling, rashes
 - pruritis (seen in Hodgkin's disease)
 - medications (can cause serum sickness → lymphadenopathy)
- physical exam
 - basic assessment: occipital, preauricular, submandibular, cervical, supra/infra-clavicular, axillary, epitrochlear, inguinal, popliteal nodes
 - ♦ characteristics of lymph nodes (Table 4)
 - ♦ look for signs of infection in regions which lymph nodes drain

- determine if lymphadenopathy is localized or generalized
- localized: typically reactive or neoplastic
 - ♦ cervical (bacterial/mycobacterial infections, ENT malignancies, metastatic cancer)
 - ♦ supraclavicular
 - right (mediastinal, bronchogenic, esophageal cancer)
 - left (gastric, gall bladder, pancreas, renal, testicular/ovarian cancer)
 - ♦ axillary (cat scratch fever, breast cancer, metastatic cancer)
 - ♦ epitrochlear (infections, sarcoidosis)
 - ♦ lower/inguinal (STDs, skin, cervix, vulva/penis, rectum/anus cancer)
- generalized: see Table 5
- thorough examination required to assess for systemic disease
- investigations
 - CBC and differential, blood film
 - ± PPD, HIV RNA, RPR/VDRL, monospot/EBV serology, ANA, imaging as indicated
 - if localized and no symptoms suggestive of malignancy, can observe 3-4 weeks (if no resolution → biopsy)
 - if generalized: lab workup; if negative → biopsy
 - if signs suggestive of malignancy, biopsy immediately
 - excisional biopsy is preferred as it preserves node architecture (essential for diagnosing lymphoma)
 - in difficult to access areas (retroperitoneal, mediastinal/hilar) multiple core biopsies may be more practical/feasible
 - FNA – helpful for diagnosing recurrence of solid tumour malignancy



Drugs That Can Cause Lymphadenopathy

Allopurinol
Atenolol
Captopril
Carbamazepine
Cephalosporins
Gold
Hydralazine
Penicillin
Phenytoin
Primidone
Pyrimethamine
Quinidine
Sulfonamides

Table 4. Inflammatory vs. Neoplastic Lymph Nodes

Feature	Inflammatory Nodes	Neoplastic
Consistency	Rubbery	Firm/hard
Mobility	Mobile	Matted/Immobile
Tenderness	Tender	Non-tender
Size	<2 cm	>2 cm

• Note: these classifications are not absolute; lymphoma and CLL nodes can feel rubbery and are frequently mobile, non-tender

Table 5. Differential Diagnosis of Generalized Lymphadenopathy

Reactive	Inflammatory	Neoplastic
Bacterial (TB, Lyme, brucellosis, cat-scratch disease)	Collagen disease (RA, dermatomyositis, lymphoma SLE, vasculitis, Sjogren)	Lymphocytic leukemias
Viral (EBV, CMV, HIV)	Drug hypersensitivity	Metastatic cancer
Parasitic (toxoplasmosis)	Sarcoidosis, amyloidosis	Histiocytosis X
Fungal (histoplasmosis)	Serum sickness	

Approach to Splenomegaly

Table 6. Differential Diagnosis of Splenomegaly

Increased Demand for Splenic Function			Congestive	Infiltrative
Hematological	Infectious	Inflammatory	Cirrhosis	Non-malignant
Spherocytosis	CMV	Felty syndrome	Splenic vein thrombosis	Benign metaplasia
Hemoglobinopathies	Bacterial endocarditis	Still's disease	Portal vein obstruction	Amyloidosis
Hemolysis	TB	SLE	CHF (right heart failure)	Lysosomal storage diseases (Gaucher's, Niemann-Pick)
Sequestration crisis	HIV/AIDS	Sarcoidosis		Glycogen storage diseases
Nutritional anemias	EBV			
Elliptocytosis	Malaria			Malignant
	Histoplasmosis			Leukemia (CML)
	Leishmaniasis			Lymphoma
				Hodgkin's disease
				Myeloproliferative disorders
				Metastatic tumour

- history
 - constitutional symptoms
 - signs or symptoms of infection or malignancy
 - history of liver disease, hemolytic anemia or high-risk exposures



Clinical Exam for Splenomegaly

JAMA 1993; 270: 2218-21

The examination for splenomegaly is most useful to rule in the diagnosis among patients in whom there is a clinical suspicion of at least 10%. Percussion is more sensitive but less specific than palpation as a diagnostic test for splenomegaly – ideally, these tests should be done together.

- physical exam
 - percussion (Castell's sign, Traube's space) and palpation
 - signs of chronic liver disease
 - associated lymphadenopathy or hepatomegaly
 - jaundice, petechiae
 - signs of CHF
- investigations
 - CBC and differential, blood film
 - as indicated: liver enzymes/liver function tests, reticulocyte count, Monospot, haptoglobin, LDH, infectious and autoimmune workups
 - imaging
 - ♦ ultrasound of abdomen/liver to rule out cirrhosis and portal vein thrombosis
 - ♦ echo for cardiac function
 - ♦ CT to rule out lymphoma



Microcytic Anemia

Table 7. Iron Indices and Blood Film in Microcytic Anemia (MCV < 80)

	Lab Tests				Blood Film
	Ferritin	Serum Iron	TIBC	RDW	
Iron Deficiency Anemia	↓↓	↓	↑	↑ (>15)	• Hypochromic, microcytic
Anemia of Chronic Disease	N/↑	↓	↓	N	• Normocytic/microcytic
Sideroblastic Anemia	N/↑	↑	N	↑	• Dual population • Basophilic stippling
Thalassemia	N/↑	N/↑	N	N/↑	• Hypochromic, microcytic • Basophilic stippling • Poikilocytosis

**Causes of Microcytic Anemia****TAILS**

Thalassemia
Anemia of chronic disease
Iron deficiency
Lead poisoning
Sideroblastic anemia



Iron Metabolism

Iron Intake (Dietary)

- “average” North American adult diet = 10-20 mg iron (Fe) daily
- absorption is 5-10% (0.5-2 mg/day); enhanced by citric acid, ascorbic acid (vitamin C) and reduced by polyphenols (e.g. in tea), phytate (e.g. in bran), dietary calcium, and soy protein
- males have positive Fe balance; up to 20% of menstruating females have negative Fe balance

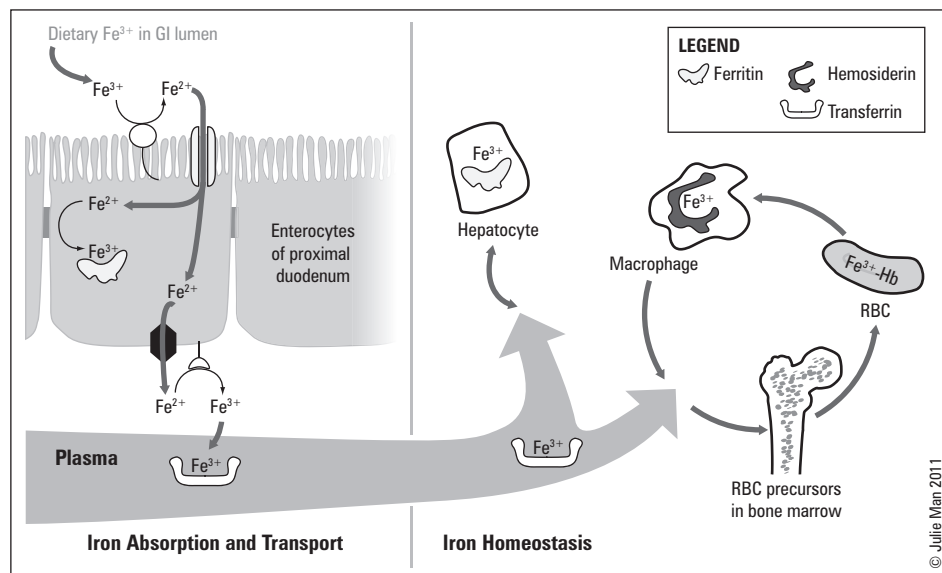


Figure 6. Iron Metabolism

Iron Absorption and Transport

- dietary iron is absorbed in the duodenum (impaired by IBD, celiac disease, etc.)
- in circulation, the majority of non-heme iron is bound to transferrin which transfers iron from enterocytes and storage pool sites (macrophages and hepatocytes) to RBC precursors in the bone marrow

Iron Storage

- ferritin
 - ferric iron complexed to a protein called apoferritin (hepatocytes are main ferritin storage site)
 - minute quantities are present in plasma in equilibrium with intracellular ferritin
 - also an acute phase reactant – can be spuriously elevated despite low Fe stores
- hemosiderin
 - aggregates or crystals of ferritin with the apoferritin partially removed
 - macrophage-monocyte system is main source of hemosiderin storage

Iron Indices (see Table 7 and Figure 7)

- bone marrow aspirate: gold standard test for iron stores
- serum ferritin: single most important blood test for iron stores
 - decreased in iron deficiency anemia
 - elevated in
 - ♦ infection, inflammation, malignancy
 - ♦ liver disease, hyperthyroidism and iron overload
- serum iron: measure of all non-heme iron present in blood
 - varies significantly daily
 - virtually all serum iron is bound to transferrin, only a trace is free or complexed in ferritin
- total iron binding capacity (TIBC): total amount of transferrin present in blood
 - normally, one third of TIBC is saturated with iron
 - high specificity for decreased iron, low sensitivity
- saturation
 - serum Fe divided by TIBC, expressed as a proportion or a percentage
 - low in iron deficiency anemia
- soluble transferrin receptor (sTfR)
 - reflects the availability of iron at the tissue level
 - the transferrin receptor is expressed on the surface of erythroblasts and is responsible for iron uptake – some is cleaved off and is present in circulation as sTfR
 - in iron deficient states, more transferrin receptor is expressed on erythroblasts, leading to an increase in sTfR
 - low in reduced erythropoiesis and iron overload
 - useful in determining iron deficiency in the setting of chronic inflammatory disorders (see *Iron Deficiency Anemia*, below)

Iron Deficiency Anemia



- most common cause of anemia in North America

Etiology

- increased demand
 - increased physiological need for iron in the body (e.g. pregnancy)
- decreased supply: dietary deficiencies (rarely the only etiology)
 - cow's milk (infant diet)
 - "tea and toast" diet (elderly)
 - absorption imbalances
 - post-gastrectomy
 - malabsorption (IBD of duodenum, celiac disease, autoimmune atrophic gastritis)
- increased losses
 - hemorrhage
 - ♦ obvious causes – menorrhagia in young women
 - ♦ occult – peptic ulcer disease, GI cancer
 - intravascular hemolysis
 - ♦ paroxysmal nocturnal hemoglobinuria (PNH)
 - ♦ cardiac valve RBC fragmentation

Clinical Features

- iron deficiency may cause fatigue before clinical anemia develops
- symptoms of anemia: fatigue, weakness, irritability, exercise intolerance, syncope, dyspnea, headache, palpitations, postural dizziness, tinnitus, feeling cold, confusion/loss of concentration
- brittle hair, nail changes [brittle, koilonychia (spoon-shaped)]
- dysphagia (e.g. esophageal web, Plummer-Vinson ring)
- pallor – conjunctiva, palmar creases
- glossitis
- angular stomatitis (inflammation and fissuring at the corners of the mouth)
- pica (appetite for non-food substances, e.g. ice, paint, dirt)

Table 8. The Utility of Ferritin in the Diagnosis of Iron Deficiency Anemia

Ferritin (µg/L)	Likelihood ratio for iron deficiency anemia
>100	0.13
45-100	0.46
18-45	3.12
≤18	41.47

Source: *Am J Med* 1990; 88:205-9

Iron deficiency anemia is a common presentation of chronic lower GI bleeds (right-sided colorectal cancer, angiodysplasia, etc.).

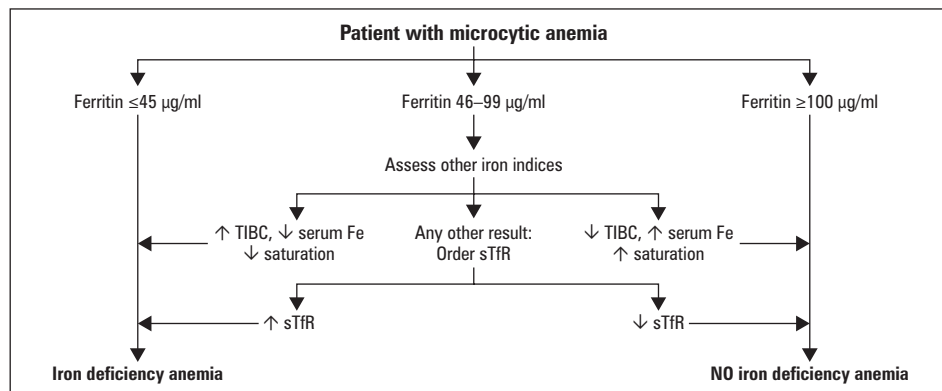
In males and in post-menopausal women, a GI work-up is always warranted.

Investigations

- iron indices, including soluble transferrin receptor (Figure 7)
 - low ferritin (<45 µg/L) is diagnostic of iron deficiency (Table 8)
 - ferritin is an acute phase protein and is elevated in the setting of inflammatory conditions and liver disease; serum ferritin <100 µg/L in these settings is suggestive of iron deficiency, necessitating further workup (Figure 7)
- peripheral blood film
 - hypochromic microcytosis: RBCs are under-hemoglobinized due to lack of iron
 - pencil forms, anisocytosis
 - target cells (thin)
- bone marrow (gold standard but not commonly done)
 - iron stain (Prussian blue) shows decreased iron in macrophages and in erythroid precursors (sideroblasts)
 - intermediate and late erythroblasts show micronormoblastic maturation

Treatment

- treat underlying cause
- supplementation
 - oral (tablets, syrup)
 - ferrous sulphate 325 mg tid, ferrous gluconate 300 mg tid, or ferrous fumarate 300 mg tid
 - supplement until anemia corrects, then continue for 3+ months until serum ferritin returns to normal
 - oral iron should be taken with citrus juice to enhance absorption
 - IV (Venofer®) can be used if patient cannot tolerate or absorb oral iron
- monitoring response
 - reticulocyte count will begin to increase after one week
 - Hb normalizes by 10 g/L per week
 - iron supplementation required for 4-6 months to replenish stores

**Figure 7. Approach to Interpreting Iron Indices**Adapted from Killip et al., *Am Fam Physician* 2007; 75:671-8

Anemia of Chronic Disease

Etiology

- infection, malignancy, inflammatory and rheumatologic disease, chronic renal and liver disease, endocrine disorders (e.g. diabetes mellitus, hypothyroidism, hypogonadism, hypopituitarism)

Pathophysiology

- an anemia of underproduction, due to impaired iron utilization
 - trapping of iron in macrophages → reduced plasma iron levels making iron relatively unavailable for new hemoglobin synthesis
 - erythropoietin levels are normal or slightly elevated, but marrow is unable to respond with increased erythropoiesis
- mild hemolytic component is often present
- RBC survival is modestly decreased

Investigations

- diagnosis of exclusion
- associated with elevation in acute phase reactants (ESR, CRP, fibrinogen)
- “classic” serum iron indices (see Table 7)
 - serum iron and TIBC low, % saturation normal
 - serum ferritin is normal or increased
- anemia of chronic disease often co-exists with iron deficiency (see sidebar)



Iron-deficiency anemia commonly co-exists with anemia of chronic disease. Suggested by:

- Serum ferritin <100 µg/L in setting of a chronic inflammatory disease
- Elevation of soluble transferrin receptor
- Absence of stainable iron on bone marrow aspiration/biopsy
- Response to a therapeutic trial of oral iron

- peripheral blood
 - mild: usually normocytic and normochromic
 - moderate: may be microcytic and normochromic
 - severe: may be microcytic and hypochromic
 - absolute reticulocyte count is frequently low, reflecting overall decrease in RBC production
- bone marrow
 - normal or increased iron stores
 - decreased or absent staining for iron in erythroid precursors

Treatment

- anemia resolves if underlying disease is treated
- only treat patients who can benefit from a higher hemoglobin
- erythropoietin may normalize the hemoglobin value

Lead Poisoning

- **L:** Lead Lines on gingivae and epiphyses of long bones on x-ray
- **E:** Encephalopathy and Erythrocyte basophilic stippling
- **A:** Abdominal colic and microcytic Anemia (sideroblastic)
- **D:** Drops (wrist and foot drop)
- treatment: dimercaprol and EDTA are first line agents



Consider lead poisoning in any child who lives in a house built before 1977.

Sideroblastic Anemia



- uncommon compared to iron deficiency anemia or anemia of chronic disease

Sideroblasts

- erythrocytes with iron-containing (basophilic) granules in the cytoplasm
- “normal”: granules are small, randomly spread in the cytoplasm
 - found in healthy individuals
- “ring”: iron deposits in mitochondria, forming a ring around the nucleus
 - abnormal, large granules
 - the hallmark of sideroblastic anemia

Etiology

- due to defects in heme biosynthesis in erythroid precursors
- hereditary (rare): X-linked; median survival 10 years
- idiopathic (acquired)
 - a.k.a. refractory anemia with ringed sideroblasts – a subtype of MDS (see *Myelodysplastic Syndrome*, H36)
 - may be a preleukemic phenomenon (10% transform to AML)
- reversible
 - drugs (isoniazid, chloramphenicol), alcohol, lead, copper deficiency, zinc toxicity, hypothyroidism

Clinical Features

- anemia symptoms (see *Iron Deficiency Anemia*, H13)
- hepatosplenomegaly, Fe overload syndrome

Investigations

- serum iron indices
 - increased serum Fe, normal TIBC, increased ferritin, increased sTfR
- blood film/bone marrow biopsy
 - ringed sideroblasts (diagnostic hallmark)
 - RBCs are hypochromic; can be micro-, normo-, or macrocytic
 - anisocytosis, poikilocytosis, basophilic stippling

Treatment

- depends on etiology
 - X-linked: high dose pyridoxine (vitamin B₆) in some cases
 - acquired: Epo and G-CSF
 - reversible: remove precipitating cause
- supportive transfusions for severe anemia

Thalassemia

- see *Hemolytic Anemia – Thalassemia*, H18



Normocytic Anemia



Causes of Normocytic Anemia

ABCD

- Acute blood loss
- Bone marrow failure
- Chronic disease
- Destruction (hemolysis)

Aplastic Anemia

Definition

- destruction of hematopoietic cells of the bone marrow leading to pancytopenia and hypocellular bone marrow

Epidemiology

- occurs at any age
- slightly more common in males

Etiology

- congenital
 - Fanconi's anemia
 - Shwachman-Diamond syndrome (bone marrow failure and pancreatic insufficiency)
- acquired
 - idiopathic
 - often T-cell mediated (1/2 to 2/3 of cases)
 - drugs
 - dose-related (e.g. chemotherapeutic agents)
 - idiosyncratic (e.g. chloramphenicol, phenylbutazone)
 - toxins
 - benzene and other organic solvents
 - DDT and insecticides
 - ionizing radiation
 - post-viral infection (parvovirus B19, EBV, HDV, HEV, HHV6, HIV)
 - autoimmune (e.g. SLE) – rare
 - paroxysmal nocturnal hemoglobinuria (PNH) – associated with aplastic anemia, but not a cause

Clinical Features

- can present acutely or insidiously
- symptoms of anemia, thrombocytopenia
- absence of splenomegaly and lymphadenopathy

Investigations

- exclude other causes of pancytopenia (Figure 3)
- CBC
 - anemia or neutropenia or thrombocytopenia (any combination) ± pancytopenia
 - decreased reticulocytes (<1% of the total RBC count)
- blood film
 - decreased number of normal RBCs
- bone marrow
 - aplasia or hypoplasia of marrow cells with fat replacement
 - decreased cellularity

Treatment

- remove offending agents
- supportive care (red cell and platelet transfusions, antibiotics)
- immunosuppression
 - anti-thymocyte globulin – 50-60% of patients respond
 - cyclosporine
- allogenic bone marrow transplant

Hemolytic Anemia (HA)



Classification

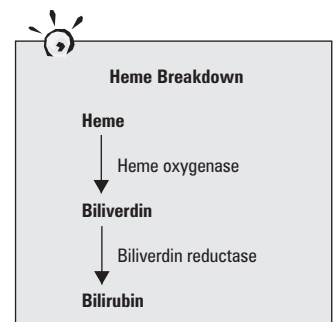
- hereditary
 - abnormal membrane (spherocytosis, elliptocytosis)
 - abnormal enzymes (pyruvate kinase deficiency, G6PD deficiency)
 - abnormal hemoglobin synthesis (thalassemias, hemoglobinopathies)
- acquired
 - immune
 - ♦ hemolytic transfusion reaction, autoimmune HA (AIHA), drugs (e.g. penicillin), cold agglutinins
 - non-immune
 - ♦ microangiopathic HA (MAHA): thrombus in blood vessel causes RBCs to be sheared
 - associated with DIC, HUS/TTP, pre-eclampsia/HELLP, vasculitides, malignant hypertension
 - ♦ other causes: PNH, hypersplenism, march hemoglobinuria (exertional hemolysis), infection (e.g. malaria), mechanical heart valves
- also classified as intravascular or extravascular:
 - intravascular: G6PD deficiency, TTP, DIC and PNH
 - extravascular: AIHA and hereditary spherocytosis

Clinical Features Specific to HA

- jaundice
- dark urine
- cholelithiasis (pigment stones)
- potential for an aplastic crisis (i.e. BM suppression in overwhelming infection)
- iron overload with extravascular hemolysis
- iron deficiency with intravascular hemolysis

Investigations

- screening tests
 - increased reticulocyte count
 - decreased haptoglobin
 - increased unconjugated bilirubin
 - increased urobilinogen
 - increased LDH
- tests specific for intravascular hemolysis
 - schistocytes on blood film
 - free hemoglobin in serum
 - methemalbuminemia (heme + albumin)
 - hemoglobinuria (immediate)
 - hemosiderinuria (delayed)
- tests specific for extravascular hemolysis
 - direct Coombs' test (direct antiglobulin test)
 - ♦ detects IgG or complement on the surface of RBC
 - ♦ add anti-IgG or anti-complement antibodies to patient RBCs; test is positive if RBCs agglutinate
 - ♦ indications
 - hemolytic disease of newborn
 - autoimmune hemolytic anemia (AIHA)
 - hemolytic transfusion reaction
 - indirect Coombs' test (indirect antiglobulin test)
 - ♦ detects antibodies in serum that can recognize antigens on RBCs
 - ♦ mix patient serum with donor RBCs and then Coombs' serum (anti-human Ig antibodies); test is positive if RBCs agglutinate
 - ♦ indications
 - cross-matching of recipient serum with donor's RBC
 - atypical blood group
 - blood group antibodies in pregnant women
 - AIHA



**Thalassemia**

β -Thal → prevalent in Mediterranean
SEA

α -Thal → prevalent in **South East Asia (SEA)**, (α = Asia, Africa)

Thalassemia

Definition

- defects in production of the alpha or beta chains of hemoglobin
 - resulting imbalance in globin chains leads to hemolysis in the spleen or BM
- clinical manifestations and treatment depends on specific gene and number of alleles affected
- common features:
 - increasing severity with increasing number of alleles involved
 - hypochromic microcytic anemia
 - basophilic stippling, abnormally shaped RBCs on blood film

Pathophysiology

- defect may be in any of the Hb genes
 - normally 4 α genes in total; 2 on each copy of chromosome 16
 - normally 2 β genes in total; 1 on each copy of chromosome 11
 - fetal hemoglobin, HbF ($\alpha_2\beta_2$), switches to adult forms HbA ($\alpha_2\beta_2$) and HbA₂ ($\alpha_2\beta_2$) at 3-6 months of life
 - HbA constitutes 97% of adult hemoglobin
 - HbA₂ constitutes 3% of adult hemoglobin

Beta-Thalassemia Minor (Thalassemia Trait)

Definition

- defect in single allele of beta gene (heterozygous)
- common in people of Mediterranean and Asian descent

Clinical Features

- palpable spleen (rare)

Investigations

- Hb 90-140 g/L or 9-14 g/dL, MCV < 70, normal Fe
- peripheral blood film – microcytosis basophilic stippling
- Hb electrophoresis
 - specific: HbA₂ increased to 2.5-5% (normal 1.5-3.5%)
 - non-specific: 50% have slight increase in HbF

Treatment

- no treatment required
- genetic counselling for patient and family

Beta-Thalassemia Major

Definition

- defect in both alleles of beta gene (homozygous, autosomal recessive)

Pathophysiology

- ineffective chain synthesis leading to ineffective erythropoiesis, hemolysis of RBCs and increase in HbF

Clinical Features

- initial presentation at age 6-12 months when HbA normally replaces HbF
 - severe anemia, jaundice
- stunted growth and development (hypogonadal dwarf)
- gross hepatosplenomegaly (due to extramedullary hematopoiesis)
- radiologic changes (due to expanded marrow cavity)
 - skull x-ray has “hair-on-end” appearance
 - pathologic fractures common
- evidence of increased Hb catabolism (e.g. pigmented gallstones)
- death can result from
 - untreated anemia (should transfuse)
 - infection (should identify and treat early)
 - iron overload: late complication secondary to repeated transfusions and ineffective erythropoiesis

**Microcytosis in Beta Thal Minor**

Microcytosis is much more profound and the anemia is much milder than that of iron deficiency.

Investigations

- Hb 40-60 g/L (4-6 g/dL)
- Hb electrophoresis
 - HbA: 0-10% (normal >95%)
 - HbF: 90-100%

Treatment

- lifelong regular transfusions + Fe chelation to prevent iron overload (e.g. deferoxamine)
- folic acid supplementation
- allogenic bone marrow transplantation

Alpha-Thalassemia

Definition

- defect(s) in alpha genes
- similar geographic distribution as beta-thalassemia but higher frequency among Asians and Africans

Clinical Features

- 1 defective α gene: clinically silent; normal Hb, normal MCV
- 2 defective α genes: decreased MCV, normal Hb
- 3 defective α genes: HbH (β_4) disease; presents in adults, decreased MCV, decreased Hb, splenomegaly
- 4 defective α genes: Hb Barts (γ_4) disease (hydrops fetalis); not compatible with life

Investigations

- peripheral blood film – screen for HbH inclusion bodies with special stain
- Hb electrophoresis not diagnostic for α -thalassemia
- DNA analysis using α gene probes

Treatment

- depends on degree of anemia:
 - 1 or 2 defective α genes: no treatment required
 - HbH disease: similar to β -thalassemia major

Sickle Cell Disease

- see Pediatrics, P49

Definition

- sickling disorders arise due to a mutant β -globin chain, most commonly caused by a Glu \rightarrow Val substitution at position 6 resulting in HbS rather than HbA
 - increased incidence of HbS allele with African or Mediterranean heritage (thought to be protective against malaria)
- sickle cell disease occurs when an individual has two HbS genes (homozygous, HbSS) or one HbS gene + another mutant β -globin gene (compound heterozygote) – most commonly HbS- β -thal and HbSC disease

Pathophysiology (Figure 8)

- at low pO_2 , deoxy HbS polymerizes leading to rigid crystal-like rods that distort membranes \rightarrow 'sickles'
- the pO_2 level at which sickling occurs is related to the percentage of HbS present
 - heterozygotes (HbAS); sickling occurs at a pO_2 of 40 mmHg
 - homozygotes (HbSS); sickling occurs at a pO_2 of 80 mmHg
- sickling aggravated by acidemia, increased CO_2 , increased 2,3-DPG, increased temperature and osmolality
- sickle cells are fragile and hemolyze; they also obstruct small vessels

Clinical Features

- HbAS (sickle cell trait): patient will be asymptomatic except during extreme hypoxia or infection
- HbSS
 - chronic hemolytic anemia
 - jaundice in the first year of life
 - retarded growth and development \pm skeletal changes
 - splenomegaly in childhood; splenic atrophy in adulthood

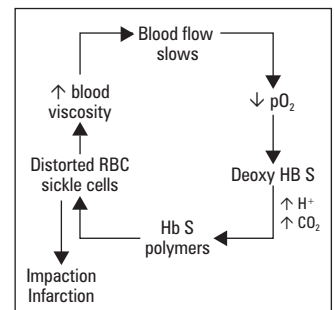


Figure 8. Pathophysiology of Sickling



Functional asplenia – increased susceptibility to infection by encapsulated organisms

- *S. pneumoniae*
- *N. meningitidis*
- *H. influenzae*
- *Salmonella* (osteomyelitis)



Acute Chest Syndrome
Affects 30% of patients with sickle cell disease and may be life threatening. Presentation includes dyspnea, chest pain, fever, tachypnea, leukocytosis, and pulmonary infiltrate on CXR. Caused by vaso-occlusion, infection, or pulmonary fat embolus from infarcted marrow.



Organs Affected by Vaso-Occlusive Crisis

Organ	Problem
Brain	Seizures, stroke
Eye	Hemorrhage, blindness
Liver	Infarcts, RUQ syndrome
Lung	Chest syndrome, long-term pulmonary hypertension
Gall bladder	Stones
Heart	Hyperdynamic flow murmurs
Spleen	Enlarged (child); atrophic (adult)
Kidney	Hematuria; loss of renal concentrating ability
Intestines	Acute abdomen
Placenta	Stillbirths
Penis	Priapism
Digits	Dactylitis
Femoral head	Avascular necrosis
Bone	Infarction, infection
Ankle	Leg ulcers

An Evidence-based Review for the NIH Consensus Development Conference on Hydroxyurea for the Treatment of Adults with Sickle Cell Disease

Ann Intern Med 2008; May 5

Objective: To synthesize the published literature on the efficacy, effectiveness, and toxicity of hydroxyurea when used in adults with sickle cell disease.

Study Selection: Randomized trials, observational studies, and case reports evaluating efficacy and toxicity of hydroxyurea in adults with sickle cell disease, and toxicity studies of hydroxyurea in other conditions that were published in English were included.

Results: In the single randomized trial, the hemoglobin level was higher in hydroxyurea recipients than placebo recipients after 2 years (difference, 6 g/L), as was fetal hemoglobin (absolute difference, 3.2%). The median number of painful crises was 44% lower than in the placebo arm. The 12 observational studies that enrolled adults reported a relative increase in fetal hemoglobin of 4% to 20% and a relative reduction in crisis rates by 68% to 84%. Hospital admissions declined by 18% to 32%. The evidence suggests that hydroxyurea may impair spermatogenesis. Limited evidence indicates that hydroxyurea treatment in adults with sickle cell disease is not associated with leukemia. Similarly, limited evidence suggests that hydroxyurea and leg ulcers are not associated in patients with sickle cell disease, and evidence is insufficient to estimate the risk for skin neoplasms, although these outcomes can be attributed to hydroxyurea in other conditions.

Conclusions: Hydroxyurea has demonstrated efficacy in adults with sickle cell disease. The paucity of long-term studies limits conclusions about toxicity.

- HbSS often presents with crisis:
 - aplastic crises
 - toxins and infections (especially parvovirus B19) transiently suppress bone marrow
 - splenic sequestration crises
 - usually in children; significant pooling of blood in spleen resulting in acute Hb drop and shock
 - uncommon in adults due to functional asplenia from repeated infarction
 - vaso-occlusive crises (infarction)
 - may affect various organs causing pain (especially in back, chest, abdomen and extremities), fever, and leukocytosis (e.g. acute chest syndrome)
 - precipitated by infections, dehydration, rapid change in temperature, pregnancy, menses and alcohol
 - chest crises (see sidebar, H19)
- HbSC (most common compound heterozygote)
 - 1:833 live births in African-Americans, common in West Africa
 - milder anemia than HbSS
 - similar complications as HbSS although typically milder and less frequent (exception is proliferative sickle retinopathy)
 - spleen not always atrophic in adults

Investigations

- sickle cell prep (detects sickling of RBCs under the microscope in response to O₂ lowering agent): determines the presence of a HbS allele
- Hb electrophoresis distinguishes HbAS, HbSS, HbSC and other variants

Table 9. Investigations for Sickle Cell Disease

	HbAS	HbSS
CBC	Normal	Increased reticulocytes, decreased Hb, decreased Hct
Peripheral blood	Normal; possibly a few target cells	Sickled cells
Hb electrophoresis	HbA fraction of 0.65 (65%) HbS fraction of 0.35 (35%)	No HbA, only HbS and HbF (proportions change with age)

Treatment

- genetic counselling
- HbAS – no treatment required
- HbSC – treatment as per HbSS, but is dictated by symptom severity
- HbSS – see Pediatrics, P50
 - folic acid to prevent folate deficiency
 - hydroxyurea to enhance production of HbF
 - mechanism of action: stops repression of Hb-gamma chains and/or initiates differentiation of stem cells in which this gene is active
 - presence of HbF in the SS cells decreased polymerization and precipitation of HbS
 - NB: hydroxyurea is cytotoxic and may cause bone marrow suppression
 - treatment of vaso-occlusive crisis
 - oxygen
 - hydration (reduces viscosity)
 - antimicrobials
 - correct acidosis
 - analgesics/narcotics
 - magnesium (inhibits potassium and water efflux from RBCs thereby preventing dehydration)
 - indication for exchange transfusion: acute chest syndrome, stroke, bone marrow necrosis, priapism, CNS crisis
 - prevention of crises
 - establish diagnosis
 - avoid conditions that promote sickling (hypoxia, acidosis, dehydration, fever)
 - vaccination in childhood (pneumococcus, meningococcus, Hib)
 - prophylactic penicillin (age 3 months-5 years)
 - good hygiene, nutrition and social support
 - screen for complications
 - regular bloodwork (CBC, reticulocytes, iron indices, BUN, LFTs, creatinine)
 - urinalysis annually
 - transcranial doppler annually until 16 years old
 - retinal examinations annually from 8 years old
 - echocardiography every two years from 10 years old (screen for pulmonary hypertension)

Autoimmune Hemolytic Anemia (AIHA)



Table 10. Classification of AIHA

	Warm	Cold
Antibody Allotype	IgG	IgM
Agglutination Temperature	37°C	4-37°C
Direct Coombs' Test (direct anti-globulin test)	Positive for IgG	Positive for complement
Etiology	Idiopathic Secondary to lymphoproliferative disorder (e.g. CLL, Hodgkin's) Secondary to autoimmune disease (e.g. SLE) Drug induced: Type I – hapten-mediated e.g. penicillin Type II – immune-complex mediated e.g. quinine Type III – “true” anti-RBC Ab e.g. methylidopa	Idiopathic Secondary to infection (e.g. mycoplasma pneumonia, EBV) Secondary to lymphoproliferative disorder (e.g. macroglobulinemia, CLL)
Blood Film	Spherocytes	Agglutination
Management	Treat underlying cause Corticosteroids Immunosuppression Splenectomy	Treat underlying cause Warm patient Immunosuppression Plasmapheresis

Microangiopathic Hemolytic Anemia (MAHA)



Definition

- hemolytic anemia due to intravascular fragmentation of RBCs

Etiology

- thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS) (see Table 17)
- DIC
- eclampsia, HELLP syndrome
- malignant hypertension
- vasculitis
- malfunctioning heart valves
- metastatic carcinoma

Investigations

- blood film: evidence of hemolysis, schistocytes
- hemolytic work-up
- urine: hemosiderinuria, hemoglobinuria

Hereditary Spherocytosis

- most common type of hereditary hemolytic anemia
- abnormality in RBC membrane proteins (e.g. spectrin)
 - spleen makes defective RBCs more spherocytotic (and more fragile) by membrane removal; also acts as site of RBC destruction
- autosomal dominant with variable penetrance
- investigations: blood film shows spherocytes, increased osmotic fragility, molecular analysis for spectrin gene
- treatment: splenectomy (pre-surgical vaccination against pneumococcus, meningococcus and Hib); avoid in early childhood

Hereditary Elliptocytosis

- abnormality in spectrin interaction with other membrane proteins
- autosomal dominant
- 25-75% elliptocytes
- hemolysis is usually mild
- treatment: immunizations; splenectomy for severe hemolysis

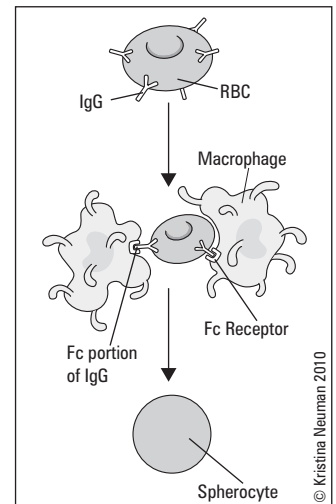


Figure 9. Spherocyte

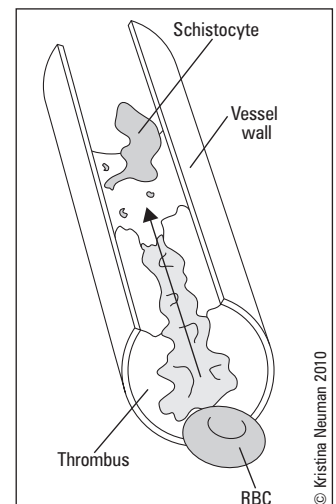


Figure 10. Schistocyte

G6PD Deficiency

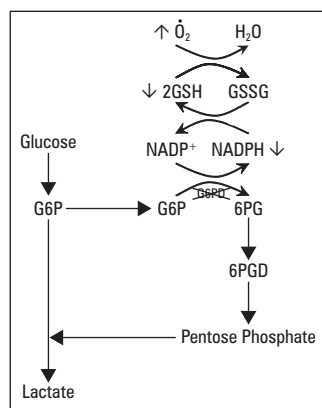


Figure 11. G6PD Deficiency

Definition

- deficiency in glucose-6-phosphate dehydrogenase (G6PD) leads to a sensitivity of RBC to oxidative stress due to a lack of reduced glutathione (GSH) (Figure 11)

Pathophysiology

- X-linked recessive, prevalent in individuals of African, Asian and Mediterranean descent

Clinical Features

- frequently presents as episodic hemolysis precipitated by:
 - oxidative stress
 - drugs (e.g. sulfonamide, antimalarials, nitrofurantoin)
 - infection
 - food (fava beans)
- in neonates: can present as prolonged, pathologic neonatal jaundice

Investigations

- neonatal screening
- G6PD assay
 - should not be done in acute crisis when reticulocyte count is high (reticulocytes have high G6PD levels)
- blood film
 - Heinz bodies (granules in RBCs due to oxidized Hb); passage through spleen results in the generation of bite cells
 - features of intravascular hemolysis (e.g. RBC fragments)

Treatment

- transfusion in severe cases
- stop offending drugs and avoid triggers

Macrocytic Anemia

- MCV >100
- see Figure 3, *Approach to Anemia*, H5

Table 11. Comparison Between Megaloblastic and Non-Megaloblastic Macrocytic Anemia

	Megaloblastic	Non-Megaloblastic
Morphology	Large, oval, nucleated RBC precursor Hypersegmented neutrophils	Large round RBC Normal neutrophils
Pathophysiology	Failure of DNA synthesis resulting in asynchronous maturation of RBC nucleus and cytoplasm	Reflects membrane abnormality with abnormal cholesterol metabolism

Vitamin B12 Deficiency

B₁₂ (cobalamin)

- binds to intrinsic factor (IF) secreted by gastric parietal cells
- absorbed in terminal ileum
- total body stores sufficient for 3-4 years

Etiology

- diet
 - strict vegan (rare, more likely to present in infants and toddlers)
- gastric
 - mucosal atrophy secondary to chronic gastritis
 - pernicious anemia (see below)
 - post-gastrectomy
- intestinal absorption
 - malabsorption (e.g. Crohn's, celiac sprue, pancreatic disease)
 - stagnant bowel (e.g. blind loop, stricture)
 - fish tapeworm
 - resection of ileum
- rare genetic causes (e.g. transcobalamin II deficiency)

Pathophysiology of Pernicious Anemia

- auto-antibodies produced against gastric parietal cells leading to achlorhydria and lack of intrinsic factor secretion
- intrinsic factor is required to stabilize B₁₂ as it passes through the bowel
- decreased intrinsic factor leads to decreased ileal absorption of B₁₂
- may be associated with other autoimmune disorders (polyglandular endocrine insufficiency)
- female:male = 1.6:1; often >60 years old

Clinical Features

- neurological
 - cerebral (common, reversible with B₁₂ therapy)
 - ♦ confusion, delirium, dementia
 - cranial nerves (rare)
 - ♦ optic atrophy
 - cord (irreversible damage)
 - ♦ subacute combined degeneration
 - posterior columns – decreased vibration sense, proprioception and 2-point discrimination
 - pyramidal tracts – spastic weakness, hyperactive reflexes
 - peripheral neuropathy (variable reversibility)
 - ♦ usually symmetrical, affecting lower limbs more than upper limbs

Investigations

- CBC, reticulocyte count
 - anemia often severe ± neutropenia ± thrombocytopenia
 - MCV > 110 fL
 - low reticulocyte count relative to the degree of anemia (<2%)
- serum B₁₂ and RBC folate
 - caution: low serum B₁₂ leads to low RBC folate because of failure of folate polyglutamate synthesis in the absence of B₁₂
- blood film
 - oval macrocytes, hypersegmented neutrophils
- bone marrow
 - hypercellularity
 - nuclear-cytoplasmic asynchrony in RBC precursors (less mature nuclei than expected from the development of the cytoplasm)
- bilirubin and LDH
 - elevated unconjugated bilirubin and LDH due to breakdown of cells in BM
- Schilling test (see sidebar) to distinguish pernicious anemia from other causes (see [Gastroenterology](#), G17)

Treatment

- vitamin B₁₂ 1000 µg IM monthly for life or 1000-1200 µg PO daily if intestinal absorption intact
- less frequent, higher doses may be as effective (e.g. 1000 µg IM q3 months)
- watch for hypokalemia and rebound thrombocytosis when treating severe megaloblastic anemia

Folate Deficiency

- uncommon in developed countries due to extensive dietary supplementation
- folate stores are depleted in 3-6 months

Etiology

- diet (folate is present in leafy green vegetables, fortified cereals)
 - traditionally most common cause (less frequent with universal supplementation in foods)
 - seen mainly in infants, elderly, alcoholics
- intestinal
 - malabsorption
- drugs/chemicals
 - alcohol
 - anticonvulsants
 - antifolates (methotrexate)
 - birth control pill
- increased demand
 - pregnancy
 - prematurity
 - hemolysis
 - hemodialysis
 - psoriasis, exfoliative dermatitis



Characteristics of Megaloblastic Macrocytic Anemia

1. Pancytopenia
2. Hypersegmented neutrophils
3. Megaloblastic bone marrow



Schilling Test

Part 1

- Tracer dose (1 µg) of radiolabeled B₁₂, given PO
- Flushing dose (1 mg) of unlabelled B₁₂ IM 1 hr later to saturate tissue binders of B₁₂ thus allowing radioactive B₁₂ to be excreted in urine
- 24 hour urine radiolabeled B₁₂ measured
- Normal > 5% excretion (a normal excretion will only be seen if the low B₁₂ was due to dietary deficiency)

Part 2

- Same as part 1, but radiolabeled B₁₂ given with oral intrinsic factor
- Should be done only if first stage shows reduced excretion
- Normal test result (> 5% excretion) = pernicious anemia
- Abnormal test result (< 5% excretion) = intestinal causes (malabsorption)

Oral Vitamin B₁₂ versus Intramuscular Vitamin B₁₂ for Vitamin B₁₂ Deficiency

Cochrane Database Syst Rev 2005; (3):CD004655

Study: Systematic review. 2 RCTs met inclusion criteria; total 108 patients with follow-up from 90 days to 4 months.

Intervention: One study evaluated 1000 µg of oral B₁₂ compared to 1000 µg IM B₁₂ on the same dosing schedule. The other compared 2000 µg daily oral B₁₂ to 1000 µg IM B₁₂ on a less frequent dosing schedule. Neurological and hematological end points were evaluated.

Results: Meta-analysis was not attempted due to study heterogeneity. Both studies reported improvements in hematological and neurological end-points in both oral and IM groups. No significant difference was observed between groups in either study.

Conclusions: High dose oral vitamin B₁₂ (1000-2000 µg) is equivalent to IM vitamin B₁₂ on the same or less frequent dosing schedule. This data is severely limited by small sample sizes and short follow-up periods. Insufficient numbers of patients with malabsorption conditions were included to generalize these results to the entire primary care population. Larger studies based in the primary care population are required.

Clinical Features

- mild jaundice due to hemolysis of RBCs secondary to ineffective hemoglobin synthesis
- glossitis and angular stomatitis
- melanin pigmentation (rare)
- purpura secondary to thrombocytopenia (rare)
- unlike B₁₂ deficiency, folate deficiency has no neurologic manifestations

Investigations

- similar to B₁₂ deficiency (CBC, reticulocytes, film, RBC folate, serum B₁₂)
- if decreased RBC folate, rule out B₁₂ deficiency as cause

Management

- folic acid 15 mg PO OD x 3 months; then 5 mg PO OD maintenance if cause not reversible



Never give folate alone to an individual with megaloblastic anemia because it will mask B₁₂ deficiency and neurological degeneration will continue.



Normal hemostasis occurs as a result of the balance between procoagulant and anticoagulant factors.

**3 Phases of Hemostasis**

1. Primary hemostasis
 - Vascular response and platelet plug formation via vWF
2. Secondary hemostasis
 - Fibrin clot formation
3. Resolution
 - Fibrinolysis

**Tests of Secondary Hemostasis**

PT/INR: Tennis is played outside (Extrinsic Pathway)

PTT: Table Tennis is played inside (Intrinsic Pathway)

Hemostasis

Three Phases of Hemostasis

1. Primary Hemostasis

- goal is rapid cessation of bleeding
- vessel injury results in collagen/subendothelial matrix exposure and release of vasoconstrictors
- blood flow is impeded and platelets come into contact with damaged vessel wall (Figure 12a)
 - adhesion: platelets adhere to subendothelium via vWF
 - activation: platelets are activated resulting in change of shape and release of ADP and thromboxane A₂
 - aggregation: these factors further recruit and aggregate more platelets resulting in formation of localized hemostatic plug

2. Secondary Hemostasis

- platelet plug is reinforced by production of fibrin clot in secondary hemostasis (Figure 12b)
- extrinsic pathway
 - initiation of coagulation in vivo
- intrinsic pathway
 - amplification once coagulation has started

3. Fibrin Stabilization and Fibrinolysis (resolution)

- conversion from soluble to insoluble clot
- once healing initiated, clot dissolution (anticoagulant pathway)

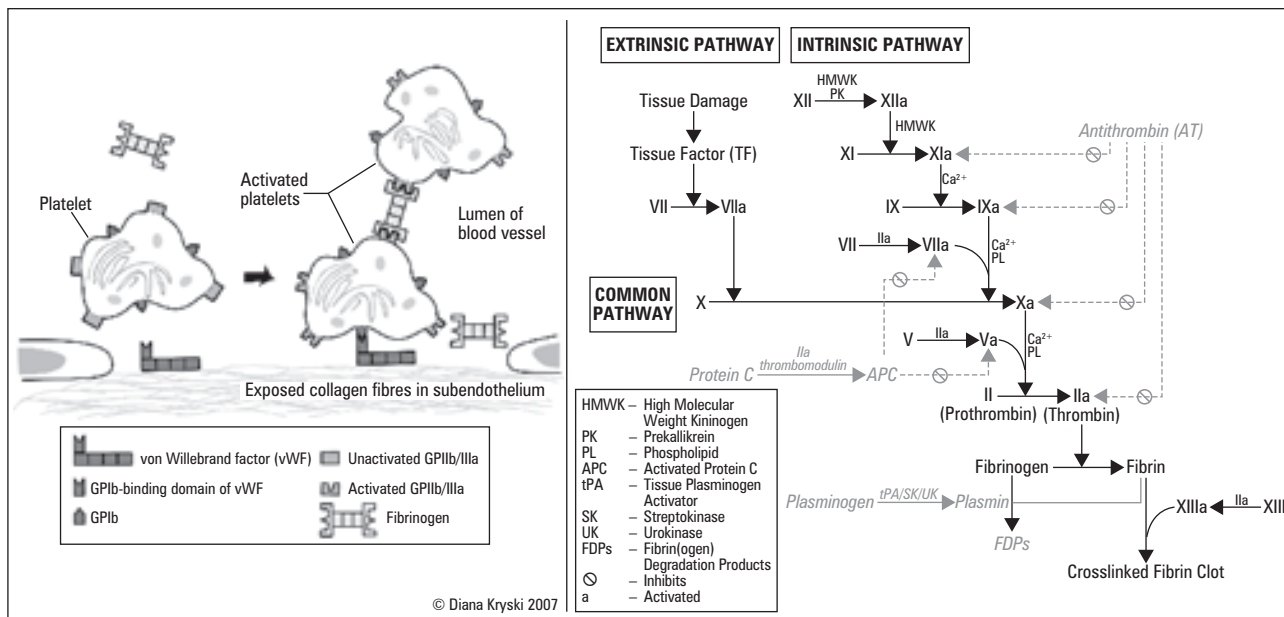


Figure 12a. Platelet Activation Cascade

Figure 12b. Coagulation Cascade

Table 12. Commonly Used Tests of Hemostasis

Type of Hemostasis	Test	Reference Range	Purpose	Examples of Associated Diagnoses
Primary	Platelet count	150-450 x 10 ⁹ /L	To quantitate platelet number	Low in ITP, HUS/TTP, DIC
	Bleeding time	N < 8 mins	Platelet function and vessel wall function	High in severe thrombocytopenia, vWD, platelet dysfunction
Secondary	aPTT	22-35 sec	Measures intrinsic pathway (factors VIII, IX, XI, XII) and common pathway Used to monitor heparin therapy	High in hemophilias A and B
	PT	11-24 sec	Measures extrinsic pathway (factor VII in particular) and common pathway	High in factor VII deficiency
	INR	0.9-1.2	Permits determination of extrinsic pathway status independent of laboratory performing measurement Used to monitor warfarin therapy	
	Mixing studies		Differentiate inhibitors of clotting factor(s) from a deficiency in clotting factor(s) Mix patient's plasma with normal plasma in 1:1 ratio and repeat abnormal test	Clotting factor(s) deficiency if test becomes normal Inhibitors of clotting factor(s) if test still abnormal
Fibrinolysis	Euglobulin lysis time	N > 9 min	Looks for accelerated fibrinolysis	May be accelerated in DIC Low in hereditary deficiency of fibrinogen
Other	Fibrinogen Fibrinogen degradation products (FDPs), D-dimers Specific factor assays Tests of physiological inhibitors (antithrombin, protein S, protein C, hereditary resistance to APC) Tests of pathologic inhibitors (e.g. lupus anticoagulant)			

Table 13. Signs and Symptoms of Disorders of Hemostasis

	Primary (Platelet)	Secondary (Coagulation)
Surface Cuts	Excessive, prolonged bleeding	Normal/slightly prolonged bleeding
Onset After Injury	Immediate	Delayed
Site of Bleeding	Superficial i.e. mucosal (nasal, gingival, GI tract, uterine), skin	Deep i.e. joints, muscles, GI tract, GU tract Excessive post-traumatic
Lesions	Petechiae, ecchymoses	Hemarthroses, hematomas

Table 14. Lab Values in Disorders of Hemostasis

	PT	PTT	Platelet Count	RBC Count
Hemophilia A/B	N	↑	N	N
vWD	N	↑	N	N
DIC	↑	↑	↓	N/↓
Liver Failure	↑	N/↑	N/↓	N
ITP	N	N	↓	N
TTP	N	N	↓	↓

Disorders of Primary Hemostasis

Definition

- inability to form an adequate platelet plug due to:
 - disorders of blood vessels
 - disorders of platelets
 - abnormal function
 - abnormal numbers (thrombocytopenia)
 - disorders of vWF

Classification

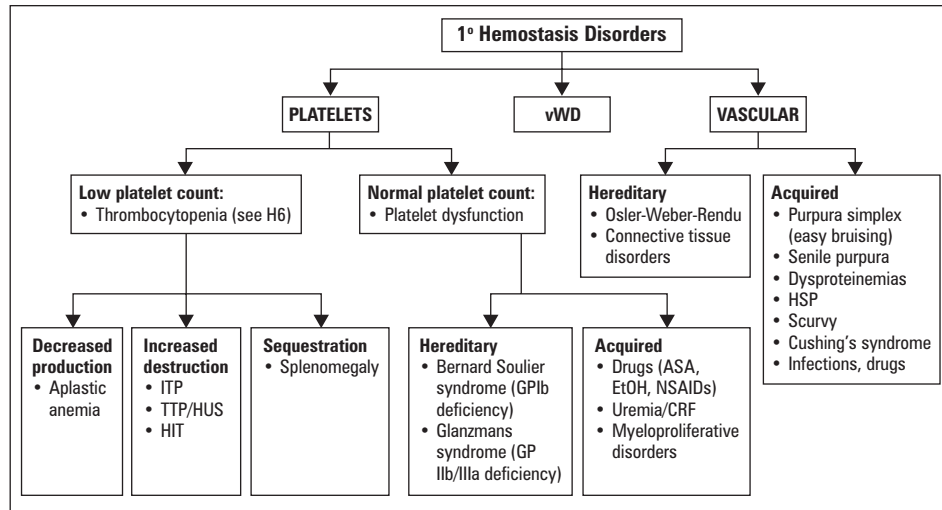


Figure 13. Approach to Disorders of Primary Hemostasis

CRF = Chronic Renal Failure



Drugs Associated with Thrombocytopenia

TMP-SMX	Heparin	NSAIDs
Vancomycin	Digoxin	Acetaminophen
Rifampin	Amiodarone	Ethanol
Ethambutol	Quinidine	H ₂ -antagonists
Amphotericin B	Quinine	



Mechanisms for HIV-associated Thrombocytopenia

- Direct effect of HIV on marrow
- Immune-mediated platelet destruction
- Some antiretrovirals reduce platelet production

Should Rituximab be Used Before or After Splenectomy in Patients with Immune Thrombocytopenic Purpura?

Curr Opin Hematol 2007; 14:642-6

Purpose: To determine whether the optimal timing for this therapy is before splenectomy, or after failure of splenectomy.

Results: No study has directly compared rituximab to splenectomy in patients with chronic immune thrombocytopenic purpura. Rituximab produces an initial response in approximately 60% of cases, with no significant difference between splenectomized and non-splenectomized patients. Long-term complete responses are observed in 15-20% of cases. Adverse events related to the drug were usually mild or moderate, with a low incidence of infections. Long-term safety data, however, are still lacking. Deaths have been reported for 2.9% of immune thrombocytopenic purpura cases treated with rituximab, but they could not be attributed to the study drug.

Conclusion: Both the response rate and the response duration appear lower following rituximab than following splenectomy. Although the side effects may be fewer, there is insufficient evidence to support the replacement of splenectomy with rituximab as a second-line treatment of chronic immune thrombocytopenic purpura outside a clinical trial. At the present time, the use of immunotherapy before splenectomy can be recommended only in patients at high risk for splenectomy and in those not willing to undergo surgery.

Immune Thrombocytopenic Purpura (ITP)

Table 15. Immune Thrombocytopenic Purpura

Features	Acute ITP	Chronic ITP
Peak Age	2-6 years	20-40 years
Sex Predilection	None	F > M (3:1)
History of Recent Infection	Common	Rare
Onset of Bleed	Abrupt	Insidious
Duration	Usually weeks	Months to years
Spontaneous Remissions	80% or more	Uncommon

ACUTE (CHILD-TYPE) ITP

- see *Pediatrics*, P51

CHRONIC (ADULT-TYPE) ITP

- most common cause of isolated thrombocytopenia
- diagnosis of exclusion (i.e. isolated thrombocytopenia with no clinically apparent cause)

Pathophysiology

- anti-platelet antibodies bind to platelet surface → increased splenic destruction and clearance

Investigations

- CBC: thrombocytopenia
- bleeding time: increased
- PT and aPTT: normal
- peripheral blood film: decreased platelets, giant platelets
- bone marrow: increased number of megakaryocytes
 - critical test to rule out other causes of thrombocytopenia for age >60 years (e.g. myelodysplasia)

Treatment**A. Emergency Treatment (active bleeding or in need of emergency surgery)**

- methylprednisolone 1 g/d for 3 days, then prednisone 1.5 mg/kg/day
- IVIG 1 g/kg/d x 2 days
- tranexamic acid 1 g IV q6h
- vaccination (pneumococcus, meningococcus, HIB)
- for life-threatening bleeding, platelet transfusions are appropriate (max. 1 pool q4-6h)
- emergency splenectomy may be considered
- management of intracranial bleeding: IV steroids, IVIG, platelets, emergency splenectomy, and then craniotomy; maintain Plt >100 for at least 7 days post ICH

B. Non-Urgent Treatment (platelet count <20-30 x 10⁹/L and no bleeding OR significant bleeding symptoms with platelet count <50 x 10⁹)

- platelet transfusion does **not** work
- avoid IVIG for patients with no active bleeding
- prednisone 1-2 mg/kg/day, taper once response is seen (Plt >50 x 10⁹) by 50% every 14 days
- all patients should be vaccinated (pneumococcus, meningococcus, HIB)
- if steroids fail, or patient relapses on taper, or requires >10 mg prednisone daily to maintain Plt >20 x 10⁹ AND has a persistent severe thrombocytopenia (<20 x 10⁹/L or 20 x 10⁹ to 50 x 10⁹ with bleeding), splenectomy may be considered

C. Post-splenectomy Refractory ITP

- dexamethasone 40 mg x 4 days, every 28 days for 6 cycles
- tranexamic acid 1 g IV tid if Plt <10 x 10⁹, active bleeding

Prognosis

- fluctuating course
- overall relatively benign, mortality 1-2%
- major concern is cerebral hemorrhage at Plt <5 x 10⁹/L, although very rare

Heparin-Induced Thrombocytopenia (HIT)**Table 16. HIT-II (Heparin-induced Thrombocytopenia, Type II)**

Pathophysiology	Immune mediated Ab recognizes a complex of heparin and platelet factor 4 (PF4) leading to platelet activation via platelet Fc receptor and activation of coagulation system
Diagnosis	50% reduction in platelets while on heparin within 5-15 days of initiation
Onset of Decreased Platelets	5-15 days (if previously exposed to heparin, HIT can develop in hours)
Risk of Thrombosis	~30% (25% of events are arterial)
Clinical Features	Bleeding complications uncommon Venous thrombosis: DVT, PE, limb gangrene, cerebral sinus thrombosis Arterial thrombosis: MI, stroke, acute limb ischemia, organ infarct (mesentery, kidney) Heparin-induced skin necrosis (w/LMWH) Acute platelet activation syndromes: acute inflammatory reactions (e.g. fever/chills, flushing, etc.) Transient global amnesia (rare)
Specific Tests	¹⁴ C serotonin release assay (uses donor platelets with ¹⁴ C serotonin and heparin with patient's plasma) ELISA for HIT-Ig (more sensitive, less specific than serotonin assay) Flow cytometry
Management	Clinical suspicion of HIT should prompt discontinuation of heparin (specific tests take several days) Because of 90% cross-reactivity, LMWH should not be substituted Alternative agents include: Lepirudin (recombinant hirudin, avoid in renal disease), Argatroban (effective thrombin inhibitor, monitored with aPTT, use with caution in liver disease), Danaparoid

Evaluation of Pretest Clinical Score (4T's) for the Diagnosis of Heparin-induced Thrombocytopenia in Two Clinical Settings*J Thromb Haemos* 2006; 4:759-65.

Study: Prospective and retrospective clinical score application in two clinical settings (Hamilton General Hospital, HGH; and Greifswald in Germany, GW).

Population: 336 patients with suspected HIT.

Intervention: Risk stratification with 4T's clinical score compared with serology for HIT antibody.

Results: 1/64 (1.6%) in HGH and 0/55 (0%) in GW with low scores tested positive on HIT serology. 8/28 (28.6%) in HGH and 11/139 (7.9%) in GW with intermediate scores tested positive for HIT. 8/8 (100%) in HGH and 9/42 (21.4%) in GW with high scores tested positive for HIT.

Conclusions: A low pretest clinical score can help to rule out HIT in patients with thrombocytopenia.



Absence of 4T's makes HIT unlikely:
Thrombocytopenia
Timing of platelet count fall
Thrombosis or other sequelae
other causes for Thrombocytopenia



LMWH is also associated with HIT but the risk is less than unfractionated heparin.

**HIT Type I (Heparin-associated thrombocytopenia)**

- Direct heparin mediated platelet aggregation (non-immune)
- Platelets > 100 X 10⁹/L
- Self-limited (no thrombotic risk)
- May continue with heparin therapy
- Onset 24-72 hours

Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS)

Table 17. TTP and HUS

	TTP	HUS
Epidemiology	Predominantly adult	Predominantly children
Etiology	Deficiency of metalloproteinase that breaks down ultra-large vWF multimers <ul style="list-style-type: none"> • Congenital (genetic absence of ADAMTS-13) • Acquired (drugs, malignancy, transplant, HIV-associated, idiopathic) 	Shiga toxin (<i>E. coli</i> serotype O157:H7)
Clinical features	<ol style="list-style-type: none"> 1. Thrombocytopenia 2. Microangiopathic hemolytic anemia (MAHA) 3. Neurological symptoms: headache, confusion, focal defects, seizures 4. Renal failure 5. Fever 	<ol style="list-style-type: none"> 1. Severe thrombocytopenia: purpura, epistaxis, hematuria, hemoptysis, GI bleed 2. Microangiopathic hemolytic anemia (MAHA) 3. Renal failure: abnormal urinalysis, oliguria, acute renal failure
Investigations (both TTP, HUS)	CBC and blood film: decreased platelets and schistocytes PT, aPTT, fibrinogen: normal Markers of hemolysis: increased unconjugated bilirubin, increased LDH, decreased haptoglobin Negative Coombs' test Creatinine, urea, to follow renal function Stool C+S (HUS)	
Management (both TTP, HUS)	Plasmapheresis ± steroids Platelet transfusion is contraindicated (increased microvascular thrombosis) Plasma infusion if plasmapheresis is not immediately available TTP mortality ~90% if untreated	



Pathophysiology of TTP

- vWF secreted by endothelial cells in a very large polymer rapidly cleaved by the ADAMTS-13 protease
- Congenital TTP is deficient in ADAMTS-13
- Antibodies against ADAMTS-13 are present in acquired TTP



Differential Diagnosis of TTP:

Sepsis
DIC
HELLP
Antiphospholipid Ab syndrome
Evans syndrome (autoimmune hemolytic anemia + ITP)



Consider vWD in all women with menorrhagia.

Von Willebrand Disease (vWD)

Pathophysiology

- heterogeneous group of defects
- usually autosomal dominant (type 3 is autosomal recessive)
- qualitative or quantitative abnormality of vWF
 - vWF needed for platelet adhesion and acts as carrier for Factor VIII; abnormality of vWF can affect both primary and secondary hemostasis
 - vWF exists as a series of multimers ranging in size
 - ♦ largest multimers are most active in mediation of platelet adhesion
 - ♦ both large and small multimers complex with Factor VIII
- usually mild in severity

Classification

- type 1: mild quantitative defect (decreased amount of vWF) – 75% of cases
- type 2: qualitative defect (dysfunctional vWF) – 20-25% of cases
- type 3: severe total quantitative defect (no vWF produced) – rare

Clinical Features

- mild
 - asymptomatic
 - mucosal and cutaneous bleeding, easy bruising, epistaxis, menorrhagia
- moderate to severe
 - as above but more severe, occasionally soft-tissue hematomas, petechiae (rare), GI bleeding, hemarthroses

Investigations

- increased bleeding time and PTT
- decreased Factor VIII (5-50%)
- platelet count normal or rarely decreased
- decreased ristocetin cofactor activity (normally causes vWF to bind platelets tightly)
- decreased von Willebrand antigen (in types 1 and 3)
- blood group (as antigen quantification reference range differs dependent on blood group)
- analysis of vWF multimers to detect variants

Treatment

- desmopressin (DDAVP®) is treatment of choice for type I vWD
 - causes release of vWF and Factor VIII from endothelial cells
 - variable efficacy depending on disease type
 - need good response before using with further bleeding
 - not to be used in type IIB (will cause worsened thrombocytopenia)
- tranexamic acid (Cyklokapron®, antifibrinolytic) to stabilize clot formation
- high-purity Factor VIII concentrate containing vWF (Hemate P®) in select cases and type
 - fresh frozen plasma (FFP) is not useful
- conjugated estrogens (increase vWF levels)

Prognosis

- may fluctuate, often improves during pregnancy and with age

Disorders of Secondary Hemostasis

Definition

- inability to form an adequate fibrin clot
 - disorders of clotting factors or co-factors
 - disorders of proteins associated with fibrinolysis
- characterized by delayed bleeding, deep muscular bleeding, spontaneous joint bleeding

Table 18. Classification of Secondary Hemostasis Disorders

Hereditary	Acquired
Factor VIII: Hemophilia A, vWD	Liver disease
Factor IX: Hemophilia B (Christmas Disease)	DIC
Factor XI	Vitamin K deficiency
Other factor deficiencies are rare	Acquired inhibitors

Hemophilia A (Factor VIII Deficiency)

Pathophysiology

- X-linked recessive, 1/5,000 males
- mild (>5% of normal factor level), moderate (1-5%), severe (<1%)

Clinical Features

- see Table 13 – *Signs and Symptoms of Disorders of Hemostasis*, H25

Investigations

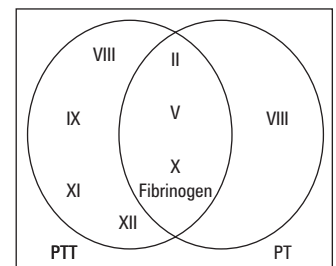
- prolonged aPTT, normal INR (PT)
- decreased Factor VIII (<40% of normal)
- vWF usually normal or increased

Treatment

- desmopressin (DDAVP®) in mild Hemophilia A
- recombinant Factor VIII concentrate for
 - prophylaxis
 - minor but not trivial bleeding (e.g. hemarthroses)
 - major potentially life-threatening bleeding (e.g. multiple trauma)
- anti-fibrinolytic agents (e.g. tranexamic acid)

**Hemophilia A****Five Hs**

Hemarthroses
Hematomas
Hematochezia
Hematuria
Head hemorrhage

**Figure 14. Clotting Factors Involved in PT and PTT**

Hemophilia B (Factor IX Deficiency)

- a.k.a. Christmas disease
- X-linked recessive, 1/30,000 males
- clinical and laboratory features identical to Hemophilia A (except decreased Factor IX)
- treatment: recombinant Factor IX concentrate, anti-fibrinolytic agents

Factor XI Deficiency

- a.k.a. Rosenthal syndrome
- autosomal recessive; more common in Ashkenazi Jews
- usually mild, often diagnosed in adulthood
- Factor XI level does not correlate with bleeding risk
- treatment: fresh frozen plasma, Factor XI concentrate

**Investigations in Liver Disease**

Factor V, VII, VIII. Expect decreased V and VII because they have the shortest half-life. Factor VIII will be normal or increased because it is produced in the endothelium.

Liver Disease

- pathophysiology
 - deficient synthesis of all factors except VIII
 - aberrant synthesis of fibrinogen
 - deficient clearance of hemostatic 'debris' and fibrinolytic activators
 - accelerated destruction due to dysfibrinogenemias: increased fibrinolysis, DIC
 - miscellaneous: inhibition of secondary hemostasis by FDPs
- investigations
 - peripheral blood film: target cells
 - primary hemostasis affected
 - ♦ thrombocytopenia 2° to hypersplenism, folate deficiency, alcohol intoxication, DIC
 - ♦ platelet dysfunction (e.g. alcohol abuse)
 - secondary hemostasis affected
 - ♦ elevated INR (PT), aPTT and thrombin time
- treatment: supportive, fresh frozen plasma, platelets, treat liver disease

Vitamin K Deficiency

Etiology

- drugs
 - oral anticoagulants inhibit Factors II, VII, IX, X, protein C and S
 - antibiotics eradicating gut flora, which provide 50% of vitamin K supply
- poor diet (especially in alcoholics)
- biliary obstruction
- chronic liver disease (decreased stores)
- malabsorption (e.g. celiac disease)
- hemorrhagic disease of newborn, see [Pediatrics](#), P73

Investigations

- INR (PT) is elevated out of proportion to elevation of the aPTT
- decreased Factors II, VII, IX and X (vitamin K-dependent)

Treatment

- hold anticoagulant
- vitamin K 1 mg PO for INR between 4.5 and 10 and not bleeding (excludes hemorrhagic disease of the newborn)
- if bleeding, give vitamin K 10 mg IV/PO
- if life-threatening bleeding, give fresh frozen plasma (FFP)
- note: excessive vitamin K will delay therapeutic warfarin anticoagulation once re-started

Disseminated Intravascular Coagulation (DIC)

Definition

- uncontrolled release of plasmin and thrombin leading to uncontrolled intravascular coagulation and depletion of platelets, coagulation factors and fibrinogen
- risk of life-threatening hemorrhage

Etiology

- occurs as a complication of many other conditions
- widespread endothelial damage ± extensive inflammatory cytokine release
- **activation of procoagulant activity**
 - antiphospholipid antibody syndrome
 - intravascular hemolysis (incompatible blood, malaria)
 - tissue injury (obstetric complications, trauma, burns, crush injuries)
 - malignancy (solid tumours, hematologic malignancies especially acute promyelocytic leukemia – AML-M3)
 - snake venom
 - fat embolism
 - heat stroke
- **endothelial injury**
 - infections/sepsis
 - vasculitis
 - metastatic disease (adenocarcinoma)
 - aortic aneurysm
 - giant hemangioma
- **reticuloendothelial injury**
 - liver disease
 - splenectomy

**Vitamin K Dependent Factors**

1972 Canada vs. Soviet
X, IX, VII, II protein C and S



PT should improve within 24 hours of vitamin K administration (onset is in 6-12 hrs). If not, search for other causes.

**Factor Levels in Acquired Coagulopathies**

Factor	Liver Disease	Vitamin K Def	DIC
V	↓	N	↓
VII	↓	↓	↓
VIII	N/↑	N	↓



DIC is a spectrum which may include thrombosis or bleeding or both.

- **vascular stasis**
 - hypotension
 - hypovolemia
 - pulmonary embolus
- **other**
 - acute hypoxia/acidosis
 - extracorporeal circulation

Clinical Features

- **signs of microvascular thrombosis**
 - neurological: multifocal infarcts, delirium, coma, seizures
 - skin: focal ischemia, superficial gangrene
 - renal: oliguria, azotemia, cortical necrosis
 - pulmonary: ARDS
 - GI: acute ulceration
 - RBC: microangiopathic hemolysis
- **signs of hemorrhagic diathesis**
 - bleeding from any site in the body 2° to decreased platelets and clotting factors
 - neurologic: intracranial bleeding
 - skin: petechiae, ecchymosis, oozing from puncture sites
 - renal: hematuria
 - mucosal: gingival oozing, epistaxis, massive bleeding

Investigations

- primary hemostasis: decreased platelets
- secondary hemostasis: prolonged INR (PT), aPTT, TT, decreased fibrinogen and other factors
- fibrinolysis: increased FDPs or D-dimers, short euglobin lysis time (i.e. accelerated fibrinolysis)
- extent of fibrin deposition: urine output, urea, RBC fragmentation

Treatment

- recognize early
- treat underlying disorder
- individualized critical care support
- in hemorrhage: replacement of hemostatic elements with platelet transfusion, FFP, cryoprecipitate
- in thrombotic phase: LMWH (controversial)



Important Etiologies of DIC

- Trauma
- Shock
- Infection
- Malignancy
- Obstetric complications



Levels of fibrinogen can still be normal in DIC as it is an acute phase reactant. Serial fibrinogen levels should be measured to see if there is a trending decrease along with an increase in D-dimer.

Table 19. Screening Test Abnormalities in Coagulopathies

Increased INR Only	Increased PTT Only	Both Increased
Factor VII deficiency	Hemophilia A and B	Prothrombin deficiency
Vitamin K deficiency	vWD	Fibrinogen deficiency
Warfarin	Heparin	Factor V and X deficiency
Liver disease	Antiphospholipid Ab	Severe liver disease
Factor VII inhibitors	Factor inhibitors	Factor V and X, prothrombin, and fibrinogen inhibitors
	F XI/F XII deficiency	Excessive anticoagulation

Venous Thrombosis

Definition

- thrombus formation and subsequent inflammatory response in a superficial or deep vein
- thrombi propagate in the direction of blood flow (commonly originating in calf veins)
- more common in lower extremity than upper extremity
- incidence ~1% if age >60
- most important sequelae are pulmonary embolism (~50% chance with proximal DVT) and chronic venous insufficiency

Etiology (Virchow's Triad)

- endothelial damage
 - leads to decreased inhibition of coagulation and local fibrinolysis
- venous stasis
 - immobilization (post-MI, CHF, stroke, post-op) inhibits clearance and dilution of coagulation factors
- hypercoagulability
 - inherited (see *Hypercoagulable Disorders*, H33)
 - acquired
 - ♦ age (risk increases with age)
 - ♦ surgery (especially orthopaedic, thoracic, GI and GU)
 - ♦ trauma (especially fractures of spine, pelvis, femur, or tibia, spinal cord injury)
 - ♦ neoplasms (especially lung, pancreas, colon, rectum, kidney and prostate)



Virchow's Triad

- Endothelial damage
- Stasis
- Hypercoagulability



Folic acid 5 mg PO daily will protect against increased homocysteine levels.

Initiating Warfarin Therapy

Ann Intern Med 2003; 138(9):714-9

Study: Multicentre, randomized trial.

Patients: 201 patients with acute venous thromboembolism.

Intervention: 5 mg warfarin initiation nomogram versus 10 mg nomogram.

Main outcomes: Time to therapeutic INR.

Results: Patients in the 10 mg group reached a therapeutic INR 1.4 days faster than those in the 5 mg group with no difference in major bleeds between the two groups ($p < 0.001$).

Conclusion: Initiation of warfarin therapy with a 10 mg nomogram allows faster achievement of a therapeutic INR without increased bleeding risk.

D-Dimer in Suspected DVT

NEJM 2003; 349(13):1227-35

Study: Multicentre, randomized trial with 16 week follow-up.

Patients: 596 patients with suspected leg DVT, stratified as either likely or unlikely to have DVT were randomized to receive or not receive D-dimer testing in addition to standard diagnostic work-ups set out by the investigators.

Results: Patients in the D-dimer tested group underwent fewer ultrasounds than those in the control group (0.78 tests per patient versus 1.34 tests per patient, $p = 0.008$). 0.4% of patients with a negative D-dimer test and no ultrasound performed were later clinically deemed to have a DVT.

Conclusion: D-dimer testing is useful in reducing the need for ultrasound in DVT diagnosis, particularly in low-risk patients.

Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer

NEJM 2003; 349:146-53

Study: RCT comparing the efficacy of LMWH (dalteparin) with an oral anti-coagulant agent (Coumarin) in preventing recurrent thrombosis in patients with cancer.

Methods: Patients with cancer who had acute, symptomatic proximal DVT, PE, or both were randomly assigned to two groups. One group received a LMWH (dalteparin 200 IU/kg SC OD) for 5-7 days and a coumarin derivative for six months (target INR, 2.5). The other group received dalteparin alone for six months (200 IU/kg 1 month, followed by a daily dose of approximately 150 IU/kg for 5 months).

Results: During the six-month study period, 27 of 336 patients in the dalteparin group had recurrent venous thromboembolism. However in the oral-anticoagulant group 53 of 336 patients (hazard ratio, 0.48; $P = 0.002$) had recurrent venous thromboembolism. The probability of recurrent thromboembolism at 6 months was 17% in the oral-anticoagulant group compared to 9% in the dalteparin group. There was no significant difference between the dalteparin and oral anticoagulant group in the rate of major bleeding (6% and 4%, respectively) or any bleeding (14% and 19%, respectively). At 6 months, the mortality rate was 39% in the dalteparin group and 41% in the oral-anticoagulant group.

Conclusions: In patients with cancer and acute venous thromboembolism, dalteparin was more effective than an oral anticoagulant in decreasing the risk of recurrent thromboembolism without increasing the risk of bleeding.

- blood dyscrasias (myeloproliferative disorders, esp. PRV, ET), PNH, hyperviscosity (multiple myeloma, polycythemia, leukemia, sickle cell)
- prolonged immobilization (CHF, stroke, MI, leg injury)
- hormone related (pregnancy, OCP, HRT, SERMs)
- antiphospholipid antibody syndrome (APLAS)
- hyperhomocysteinemia
- heart failure (risk of DVT greatest with right heart failure and peripheral edema)

- idiopathic (10-20% are later found to have cancer)

Clinical Features

- absence of physical findings does not rule out disease
- unilateral leg edema, erythema, warmth and tenderness
- palpable cord (thrombosed vein)
- phlegmasia cerulea dolens and phlegmasia alba dolens with massive thrombosis
- Homan's sign (pain with foot dorsiflexion) is unreliable

Differential Diagnosis

- muscle strain or tear, lymphangitis or lymph obstruction, venous valvular insufficiency, ruptured popliteal cysts, cellulitis, arterial occlusive disease

Investigations

- D-dimer test only useful to rule out DVT if negative and low clinical suspicion of disease
- doppler ultrasound is most useful diagnostic test for DVT
 - sensitivity and specificity for proximal DVT ~95%
 - sensitivity for calf DVT ~70%
- other non-invasive tests include MRI and impedance plethysmography
- venography is the gold standard, but is expensive, invasive and higher risk

Approach to Treatment of Venous Thrombosis

Purpose

- prevent further clot extension
- prevent acute pulmonary embolism (occurs in ~50% of untreated patients)
- reduce the risk of recurrent thrombosis
- treatment of massive iliofemoral thrombosis with acute lower limb ischemia and/or venous gangrene (phlegmasia cerulea dolens)
- limit development of late complications, e.g. postphlebitic syndrome, chronic venous insufficiency and chronic thromboembolic pulmonary HTN

Initial Treatment

- unfractionated heparin (UFH)
 - requires bolus (7500-10,000 IU), followed by continuous IV infusion (1000-1500 IU/h)
 - weight-based heparin nomograms help to achieve proper dosing
 - advantages: rapidly reversible by protamine
 - disadvantages: must monitor aPTT with adjustment of dose to reach therapeutic level (~2x normal value); monitor platelet counts for development of HIT
- low molecular weight heparin (LMWH)
 - administered SC, at least as effective as UFH
 - advantages: predictable dose response and fixed dosing schedule; lab monitoring not required; lower risk of HIT; safe and effective outpatient therapy
 - disadvantages: only partially reversible by protamine
 - ♦ renally cleared – may need to adjust dose in patients with renal dysfunction
- alternatives to LMWH and UFH
 - heparinoids (patients with HIT), direct thrombin inhibitors (hirudin, lepirudin, argatroban), Factor Xa inhibitors (fondaparinux)
 - thrombolytic drugs (e.g. streptokinase, tPA) reserved for limb/life-threatening thrombosis, recent symptoms, low bleeding risk

Long-term Treatment

- warfarin
 - standard treatment; should be initiated with heparin overlap – dual therapy for at least 5 days
 - discontinue heparin after INR > 2.0 for two consecutive days
 - warfarin should be dosed to maintain INR at 2-3 except in select cases
 - monitor INR twice weekly for 1-2 weeks, then weekly until INR stable, then every 2-4 weeks
 - recent evidence suggests therapeutic INR can be reached quicker with warfarin initiation protocol that starts with 10 mg dose (see sidebar)
 - LMWH more effective than warfarin at preventing recurrence of venous thrombosis in cancer patients (see sidebar)
- duration of anticoagulant treatment (with warfarin unless otherwise noted):
 - first episode DVT with transient risk factor: 3 months
 - first episode DVT with ongoing risk factor (e.g. cancer, antiphospholipid antibody) or > 1 risk factor: consider indefinite therapy

- first episode DVT with no identifiable risk factor (idiopathic) or single inherited risk factor (e.g. Factor V Leiden): 6-12 months or indefinite therapy (controversial)
- recurrent DVT (2 or more episodes): indefinite therapy
- IVC filters
 - useful in those with contraindications to anticoagulant therapy, recurrent thromboembolism despite adequate anticoagulation, chronic recurrent embolism with pulmonary HTN, or those who require emergent surgery without time to initiate anticoagulation
- special considerations
 - pregnancy: treat with LMWH during pregnancy, then warfarin for 4-6 weeks post-partum (minimum total anticoagulation time of 3-6 months)
 - surgery: avoid elective surgery in the first month after a venous or arterial thromboembolic event
 - ♦ preoperatively: IV heparin may be used up to 6 hours pre-operatively
 - ♦ perioperatively: surgery safe when INR <1.5; warfarin should be discontinued for at least 4 days pre-operatively to allow INR to fall
 - ♦ postoperatively: IV heparin or LMWH can be used for anticoagulation (start 12 hours after major surgery until therapeutic INR reached after restarting warfarin)
 - ♦ for patients at high risk for thromboembolism (VTE <12 weeks, recurrent VTE, lupus anticoagulant, atrial fibrillation with prior stroke, mechanical heart valve), intravenous heparin or LMWH (bridging) should be given before and after the procedure while the INR is below 2.0

Prophylaxis

- consider for those with a moderate to high risk of thrombosis without contraindications
- non-pharmacological measures include: early ambulation, elastic compression stockings (TEDs), intermittent pneumatic compression (IPC)
- UFH 5000 IU SC bid for moderate risk
- UFH 5000 IU SC tid or enoxaparin 40 mg SC OD for high risk

Contraindications and Adverse Reactions of Anticoagulant Therapy

- see *Anticoagulant Therapy*, H55

Treatment of Pulmonary Embolism (PE)

- see *Respirology*, R19

Hypercoagulable Disorders

Hypercoagulability Workup – Venous Thrombosis

- workup for malignancy or hypercoagulable state indicated for idiopathic VTE in presence of the following features: age <50, recurrent VTE, family history of VTE, unusual site of DVT (portal, hepatic, mesenteric vascular beds), heparin-resistant disease (AT deficiency), warfarin-induced skin necrosis or neonatal purpura fulminans (Protein C or S deficiency)
- workup:
 - initial
 - ♦ CBC, blood smear, coagulation studies, liver/renal function, urinalysis, fasting homocysteine
 - ♦ malignancy work up (see sidebar, H34)
 - ♦ APLA: ACA (anticardiolipin antibodies) and LA (lupus anticoagulant)
 - ♦ APCR (activated Protein C resistance)
 - ♦ DNA: FVL (Factor V Leiden), PT (prothrombin G20210A), MTHFR (5,10-methylenetetrahydrofolate reductase)
 - after the acute event
 - ♦ antithrombin (not on heparin)
 - ♦ FVIII (increased levels predict recurrence)
 - post-treatment
 - ♦ Protein C, S (not on warfarin)

CAUSES OF HYPERCOAGULABILITY LEADING TO VENOUS THROMBOEMBOLISM

Activated Protein C Resistance (Factor V Leiden)

- most common cause of hereditary thrombophilia
- 5% of general population are heterozygotes
- point mutation in the Factor V gene (R506Q) results in resistance to inactivation of Factor Va by activated Protein C

Prothrombin (PT) G20210A

- G to A transposition at nucleotide position 20210 of the prothrombin gene promoter region results in increased levels of prothrombin, thus increased thrombin generation

Duration of Treatment with Vitamin K Antagonists in Symptomatic Venous Thromboembolism

Cochrane Database of Systematic Reviews 2006; Issue 1

Study: Meta-analysis of 8 RCTs (2994 patients) comparing different durations of treatment with vitamin K antagonists in patients with symptomatic venous thromboembolism (VTE).

Main Results: In patients treated with vitamin K antagonists for a prolonged period, the reduction in risk of recurrent VTE remained consistent regardless of the period of time since the index event (OR 0.18, CI 0.13-0.26). In addition, there was no observed excess of VTE recurrences following cessation of prolonged vitamin K antagonist therapy (OR 1.24, CI 0.91-1.69). However, patients who received prolonged treatment had a persistent increase in their risk of major bleeding complications (OR 2.61, CI 1.48-4.61).

Conclusion: Prolonged treatment with vitamin K antagonists leads to a consistent reduction in the risk of recurrent VTE for as long as therapy is continued. Therapy should be discontinued when the risk of harm from major bleeding (which remains constant over time) is of greater concern than the absolute risk of recurrent VTE (which declines over time). No specific recommendation was made regarding optimal duration of treatment.



Initiation of Warfarin Therapy Requires Overlap with Heparin Therapy for 4-5 Days

- 10 mg loading dose of warfarin causes a precipitous decline in Protein C levels in 1st 36 hours resulting in a transient hypercoagulable state.
- Warfarin decreases Factor VII levels in 1st 48 hrs → INR is prolonged (most sensitive to Factor VII levels), however full antithrombotic effect is not achieved until Factor IX, X, and II are sufficiently reduced (occurs after approx. 4 days).



Low risk surgical patients:

<40 yrs, no risk factors for VTE, general anesthetic (GA) <30 mins, minor elective, abdominal or thoracic surgery.

Moderate risk surgical patients:

>40 yrs, >1 risk factor for VTE, GA >30 mins.

High risk surgical patients:

>40 yrs, surgery for malignancy or lower extremity orthopedic surgery lasting >30 mins, inhibitors deficiency or other risk factor.

High risk medical patients: heart failure, severe respiratory disease, ischemic stroke and lower limb paralysis, confined to bed and have >1 additional risk factor (e.g. active cancer, previous VTE, sepsis, acute neurologic disease, IBD).



Common Causes of Hypercoagulability

CALMSHAPE

Protein C deficiency
Antiphospholipid Ab
Factor V Leiden
Malignancy
Protein S deficiency
Increased Homocysteine
Antithrombin deficiency
Prothrombin G20210A
Increased Factor VIII (Eight)



Although lupus anti-coagulant prolongs PTT, its main clinical feature is thrombosis.



Protein C, Protein S, and ATIII are decreased during acute thrombosis – therefore to test for deficiency, must be tested outside of this time period.



Causes of Both Venous and Arterial Thrombosis include:

- Antiphospholipid antibodies
- Hyperhomocysteinemia
- Myeloproliferative disorders
- Heparin induced thrombocytopenia



Malignancy is a Common Acquired Cause of Hypercoagulability.

Workup includes:

- Complete history and physical
- Routine bloodwork
- Urinalysis
- CXR
- Mammogram and Pap in females
- PSA in males
- Colonoscopy
- Close follow-up



Typical Age of Presentation of Leukemias

ALL – Children
CML – 40-60 yrs
AML, CLL – 60+ years



Leukemia – malignant cells arise in bone marrow and may spread elsewhere (including lymph nodes and lymphoid tissue)

Lymphoma – malignant cells arise in lymph nodes and lymphoid tissues and may spread elsewhere (including bone marrow)

BUT: the location where the malignant cells are found does not define the type of hematologic malignancy – classified based on the characteristics of the cell (histology, histochemistry, immunophenotyping, cytogenetics, molecular changes)

Hyperhomocysteinemia

- both a genetic and acquired abnormality
- increased homocysteine levels are found in vitamin B₁₂, B₆ and folate deficiencies, chronic renal failure, hypothyroidism, malignancy, methotrexate, phenytoin, theophylline
- folate 5 mg/day can decrease plasma homocysteine by 50% (effect on thrombosis risk unclear)
- also increases risk of arterial thrombosis

Protein C and Protein S Deficiency

- Protein C inactivates Factor Va and VIIIa using Protein S as a cofactor
- Protein C deficiency
 - homozygous: neonatal purpura fulminans
 - heterozygous:
 - ♦ type I: decreased Protein C levels
 - ♦ type II: decreased Protein C activity
 - acquired: liver disease, sepsis, DIC, warfarin
 - 1/3 of patients with warfarin necrosis have underlying Protein C deficiency
- Protein S deficiency
 - type I: decreased free and total Protein S levels
 - type II: decreased Protein S activity
 - type III: decreased free Protein S levels
 - acquired: liver disease, DIC, pregnancy, nephrotic syndrome, inflammatory conditions, warfarin

Antithrombin Deficiency

- antithrombin slowly inactivates thrombin in the absence of heparin, rapidly inactivates thrombin in the presence of heparin
- autosomal dominant inheritance or urinary losses in nephrotic syndrome
- type I: decreased AT levels; type II: decreased AT activity
- diagnosis must be made outside window of acute thrombosis and anticoagulation treatment (acute thrombosis, heparin, systemic disease all decrease antithrombin levels)
- deficiency may result in resistance to unfractionated heparin (LMWH must be used)

Elevated Factor VIII Levels

- an independent marker of increased thrombotic risk
- genetic basis for increased levels poorly understood

Disorders of Fibrinolysis

- include congenital plasminogen deficiency, tissue plasminogen activator deficiency

Antiphospholipid Antibody Syndrome (APLAS)

- definition: ≥1 clinical and ≥1 laboratory criteria
- clinical: thrombosis, spontaneous abortions, fetal loss, premature birth before 34 wks
- laboratory: anticardiolipin or lupus anticoagulant antibodies
- mechanism: not well understood, interact with platelet membrane phospholipid and increased adhesion and aggregation; also can interfere with action of protein C and S

Hematologic Malignancies and Related Disorders

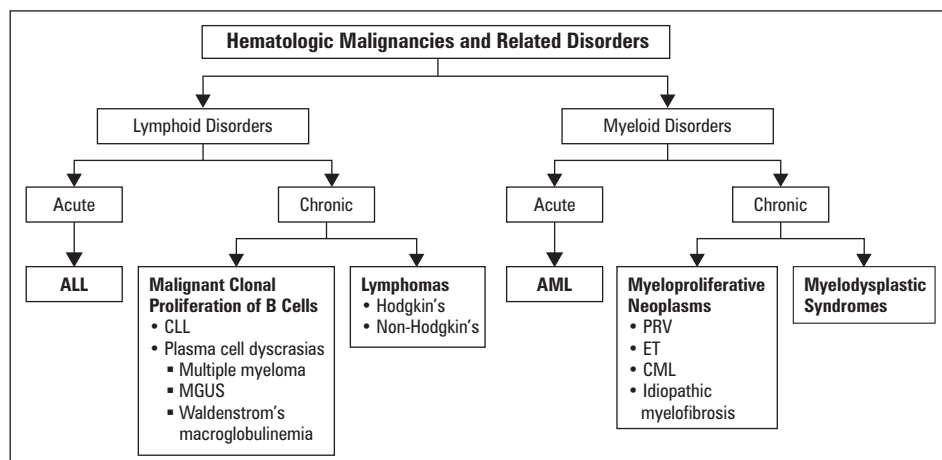


Figure 15. Overview of Hematologic Malignancies and Related Disorders

Myeloid Malignancies

Acute Myeloid Leukemia (AML)

Definition

- rapidly progressive malignancy characterized by failure of myeloid cells to differentiate beyond blast stage

Epidemiology

- incidence increases with age; median age of onset is 65 years old
- accounts for 10-15% of childhood leukemias

Risk Factors

- myelodysplastic syndromes (MDS), benzene, radiation, alkylating agents for previous malignancy

Pathophysiology

- etiology subdivided into:
 - primary – *de novo*
 - secondary – hematologic malignancies (e.g. myeloproliferative disorders and MDS) or previous chemotherapeutic agents (e.g. alkylating agents)
- uncontrolled growth of blasts in marrow leads to:
 - suppression of normal hematopoietic cells
 - appearance of blasts in peripheral blood
 - accumulation of blasts in other sites
 - metabolic consequences of a large tumour mass

Clinical Features

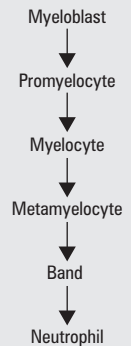
- anemia
- thrombocytopenia (associated with DIC in promyelocytic leukemia)
- neutropenia (even with normal WBC): leads to infections, fever
- accumulation of blast cells in marrow
 - skeletal pain, bony tenderness (especially sternum)
- organ infiltration
 - gingival hypertrophy – may present to dentist first
 - splenomegaly – early satiety, LUQ fullness
 - hepatomegaly
 - lymphadenopathy (not marked)
 - skin – leukemia cutis
 - gonads
 - eyes – Roth spots, cotton wool spots, vision changes (uncommon)
- leukostasis/hyperleukosis syndrome (medical emergency)
 - large numbers of blasts interfere with circulation and lead to hypoxia and hemorrhage – can cause diffuse pulmonary infiltrates, CNS bleeding, respiratory distress, altered mental status
- metabolic effects; aggravated by treatment (rare)
 - increased uric acid → nephropathy, gout
 - release of phosphate → decreased Ca, decreased Mg
 - release of procoagulants → DIC
- decreased or normal K before treatment, increased K after treatment

Investigations

- bloodwork
 - CBC – anemia, thrombocytopenia, variable WBC
 - INR, aPTT, FDP, fibrinogen (in case of DIC)
 - increased LDH, increased uric acid, increased PO_4 (released by leukemic blasts), decreased Ca
 - baseline RFTs, LFTs
- peripheral blood film – circulating blasts with Auer rods (azurophilic granules)
- bone marrow aspirate
 - blast count: AML >20% (normal is <5%)
 - histologic classification (French-American-British (FAB) → M0-M7) – based on stage at which cell differentiation stops (see sidebar)
 - cytogenetics, immunophenotyping
- CXR to r/o pneumonia, ECG, MUGA scan prior to chemotherapy (cardiotoxic)



Neutrophil Maturation*



*AML can involve any myeloid lineage



Acute Leukemia

Definition – (WHO) Presence of 20% blast cells or greater in bone marrow at presentation.

Classification – divided into myeloid (AML) and lymphoid (ALL), depending on whether blasts are myeloblasts or lymphoblasts, respectively.



Auer rods are pathognomonic for AML.



French-American-British (FAB) Classifications

Subtype	Freq	Common Name
M0	<5%	Minimally differentiated
M1	20%	Myeloblastic without maturation
M2	25%	Myeloblastic with maturation
M3	10%	Promyelocytic (APML)
M4	20%	Myelomonocytic
M5	20%	Monocytic
M6	5%	Erythroleukemic
M7	<5%	Megakaryoblastic



Cure: survival that parallels age-matched population

Complete Remission: tumour load below threshold of detectable disease (normal peripheral blood film, normal bone marrow with <5% blasts, normal clinical state)

Treatment

- mainstay of treatment is chemotherapy (rapidly fatal without treatment)
 - all AML subtypes treated similarly except promyelocytic variant with t(15:17) translocation – all-trans-retinoic acid (ATRA) added to induce differentiation
- treatment strategy
 - 1. Induction** – chemotherapy to induce complete “remission” of AML (see sidebar)
 - several possible regimens [e.g. cytarabine with anthracycline (daunorubicin)]
 - patients with poor response to initial induction therapy – poorer prognosis
 - 2. Consolidation** – to prevent recurrence
 - intensive consolidation chemotherapy
 - stem cell transplantation – autologous or allogeneic (younger patients with better performance status)
- consider acceleration with hematopoietic growth factors (e.g. G-CSF) if increased incidence of severe infection
- supportive care
 - screening for infection via regular C&S of urine, stool, sputum, oropharynx, catheter sites, perianal area
 - fever – C&S of all orifices, CXR, start antibiotics
 - platelet and RBC transfusions (irradiated to prevent transfusion-related GVHD) ± Epo
 - prevention and treatment of metabolic abnormalities
 - allopurinol for prevention of hyperuricemia

Prognosis

- achievement of first remission
 - 70-80% if 60 years old, 50% if >60 years old
 - median survival 12-24 months
 - 5 year survival 40%
- survival may be improved by bone marrow transplant (BMT) – 50-60% cure rate
- adverse prognostic factors: age >60, poor performance score before treatment, AML secondary to chemotherapy or MDS/chronic myeloproliferative disorder, WBC >20 000/cm³, increased LDH, unfavourable cytogenetics (e.g. monosomy or deletion of chromosomes 5 or 7)

Myelodysplastic Syndromes (MDS)



WHO MDS Classification

- Refractory anemia (RA)
- Refractory anemia with ringed sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)
- Refractory anemia with excess blasts I and II
- 5q- syndrome (MD with del(5q))
- Myelodysplasia unclassified (seen in cases of megakaryocyte dysplasia with fibrosis and others)



MDS is a cause of macrocytic anemia.



Myelodysplastic Syndromes:
ineffective maturation

Myeloproliferative Neoplasms:
overproduction of mature cells

Definition

- heterogeneous group of malignant stem cell disorders characterized by dysplastic and ineffective blood cell production resulting in peripheral cytopenias
- syndromes defined according to French-American-British (FAB) or World Health Organization (WHO) classifications

Pathophysiology

- disordered maturation – ineffective hematopoiesis despite presence of adequate numbers of progenitor cells in bone marrow (usually hypercellular)
- intramedullary apoptosis – programmed cell death within bone marrow
 - both processes lead to reduced mature cells in periphery
- 30-40% develop AML

Risk Factors

- elderly, post-chemotherapy, benzene or radiation exposure
- occurs in 49-89/100,000 in patients >60 years old

Clinical Features

- insidious onset
- fatigue, weakness, pallor, infections, bruising, epistaxis
- rarely: weight loss, fever, hepatosplenomegaly
- infections and bleeding out of proportion with peripheral blood counts

Investigations

- diagnosed by
 - anemia ± thrombocytopenia ± neutropenia
 - bone marrow hypercellularity with tri-lineage dysplastic changes (dysmyelopoiesis, dyserythropoiesis, dysthrombopoiesis)
- CBC and peripheral blood film
 - RBC: usually macrocytic with oval shaped red cells (macro-ovalocytes), decreased reticulocyte count
 - WBC: decreased granulocytes and abnormal morphology (e.g. bilobed or unsegmented nuclei = Pelger abnormality)
 - platelets: thrombocytopenia, abnormalities of size and cytoplasm (e.g. giant hypogranular platelets)

- bone marrow aspirate and biopsy with cytogenetic analysis required for definitive diagnosis
 - bone marrow – normocellular/hypercellular (but 10% hypocellular), often with micromegakaryocytes; 10% have marrow fibrosis
 - ♦ may see ring sideroblasts in varying proportion
 - cytogenetics – partial or total loss of chromosomes 5, 7, Y, or trisomy 8

Prognosis

- the MDS International Prognostic Scoring System (IPSS) uses 3 factors to estimate mean survival:
 - the percentage of bone marrow blasts, the karyotype and the number of cytopenias
 - based on the calculated score, a patient's MDS is categorized as “low”, “intermediate 1”, “intermediate 2”, or “high” with a mean survival of 0.4, 3.5, 1.2 and 5.7 years respectively

Treatment

- **low risk** of transformation to acute leukemia (IPSS low and intermediate 1)
 - supportive care: RBC and platelet transfusion, antibiotics, antifungals
 - erythropoietin SC weekly may be effective in reducing transfusion requirements
 - hematopoietic growth factors (G-CSF, GM-CSF) may decrease risk of infection
- **high risk** of transformation to acute leukemia (IPSS intermediate 2 and high)
 - supportive care
 - stem cell transplantation
 - AML-type chemotherapy
 - epigenetic therapy: DNA methyltransferase inhibitors (e.g. 5-Azacytidine), histone deacetylase inhibitors
 - angiogenesis inhibitors
 - arsenic trioxide
 - farnesyl transferase inhibitors

Use of Epoetin and Darbepoetin in Patients with Cancer

Blood 2008 ;111:25-41

Clinical practice guideline update by American Societies of Hematology and Clinical Oncology (2007)

Recommendations:

- 1) Initiate an erythropoiesis-stimulating agent (ESA) when hemoglobin (Hb) is near or below 100 g/L (10 g/dL) in patients with chemotherapy-associated anemia to decrease the need for transfusions.
- 2) Same as #1 for patients with low-risk myelodysplasia.
- 3) Follow the package insert for dose initiation and modification.
- 4) Discontinue ESAs when patient not responding to treatment beyond 6 to 8 weeks.
- 5) Monitor iron stores and supplement iron intake for ESA-treated patients when necessary.
- 6) Use ESAs cautiously with chemotherapy or in patients with an elevated risk for thromboembolic complications.
- 7) ESA should not be used for patients with cancer who are not receiving chemotherapy, as it increases thromboembolic risks and lowers survival rate.

Myeloproliferative Neoplasms (MPNs)

Definition

- clonal myeloid stem cell abnormalities leading to overproduction of one or more cell lines (leading to abnormalities in erythrocytes, platelets and other cells of myeloid lineage)

Epidemiology

- mainly middle-aged and older patients (peak 60-80 years)

Prognosis

- may develop marrow fibrosis with time
- all disorders may progress to AML

Table 20. Chronic Myeloproliferative Disorders

	PV	CML	IMF	ET
Hct	↑↑	↓/N	↓	N
WBC	↑	↑↑	↑/↓	N
Plt	↑	↑/↓	↑/↓	↑↑↑
Marrow fibrosis	±	±	+++	±
Splenomegaly	+	+++	+++	+
Hepatomegaly	+	+	++	–
Genetic Association	JAK2 mut. (95%)	Bcr-Abl mut. (90+%)	JAK2 mut. (~50%)	JAK2 mut. (~50%)

PV = polycythemia vera CML = chronic myeloid leukemia IMF = idiopathic myelofibrosis ET = essential thrombocythemia



Basophilia is uncommon in other medical conditions.



Erythromelalgia is a pathognomonic microvascular thrombotic complication in PRV and ET.

Polycythemia Rubra Vera (PRV)

Definition

- stem cell disorder characterized by elevated RBC mass (erythrocytosis) accompanied by increased white cell and platelet production

Clinical Features

- those secondary to high red cell mass and hyperviscosity (see *Polycythemia*, H5)
- bleeding complications: epistaxis, gingival bleeding, ecchymoses and GI bleeding
 - due to platelet abnormalities
- thrombotic complications: DVT, PE, thrombophlebitis, increased incidence of stroke, MI
 - due to increased blood viscosity, increased platelet number and/or activity
- erythromelalgia (burning pain in hands and feet)
 - associated with platelets $>400 \times 10^9/L$
 - pathognomonic microvascular thrombotic complication in PRV and ET
- pruritus, especially after warm bath or shower (40%)
 - due to cutaneous mast cell degranulation and histamine release
- epigastric distress, PUD
 - due to increased histamine from tissue basophils, alterations in gastric mucosal blood flow due to increased blood viscosity
- gout (hyperuricemia)
 - due to increased cell turnover
- characteristic physical findings
 - plethora (ruddy complexion) of face (70%), palms
 - splenomegaly (70%), hepatomegaly (40%)

Investigations

- see *Polycythemia*, H5
- must rule out secondary polycythemia
- diagnosis (WHO) involves two required (*) A criteria + 1 other A or 2 B criteria
 - **A Criteria (Major)**
 - ♦ elevated red cell mass* ($>25\%$ above mean predicted value)
 - ♦ no cause of 2° erythrocytosis * (i.e. arterial $PO_2 >92\%$)
 - ♦ palpable splenomegaly
 - ♦ clonal genetic abnormality other than bcr-abl fusion gene
 - ♦ endogenous erythroid colony formation in vitro
 - **B Criteria (Minor)**
 - ♦ thrombocytosis ($>400 \times 10^9/L$)
 - ♦ leukocytosis ($>12 \times 10^9/L$)
 - ♦ bone marrow biopsy revealing panmyelosis with erythroid and megakaryocytic proliferation
 - ♦ low serum EPO level
- JAK2 mutation identified in most cases

Treatment

- phlebotomy to keep hematocrit $<45\%$
- hydroxyurea (age >65 , prior thrombosis or symptoms), ^{32}P (age >80 or lifespan <10 years)
- low-dose aspirin (for erythromelalgia and/or antithrombotic prophylaxis)
- allopurinol – as needed
- antihistamines – as needed

Prognosis

- 10–20 year survival with treatment
- complicated by thrombosis, hemorrhage, leukemic transformation (AML)

Chronic Myeloid Leukemia (CML)

Definition

- myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate

Epidemiology

- generally presents in fourth or fifth decade of life

Pathophysiology

- Philadelphia chromosome (Ph)
 - translocation between chromosomes 9 and 22
 - the **c-abl** proto-oncogene is translocated from chromosome 9 to “breakpoint cluster region” (bcr) of chromosome 22 to produce *bcr-abl* fusion gene, an active tyrosine kinase

Efficacy and Safety of Low-dose Aspirin in Polycythemia Vera

NEJM 2004; 350:114-24

Study: Double-blind, placebo-controlled, randomized trial.

Participants: 518 patients with polycythemia vera with no clear indication for or contraindication to aspirin therapy.

Intervention: Patients received either low-dose aspirin 100 mg daily (n=253) or placebo (n=265) and were followed for up to 5 years.

Primary Outcome: Cumulative rate of (I) nonfatal MI, nonfatal stroke, or death from cardiovascular causes and the cumulative rate of (II) the previous 3 plus pulmonary embolism and major venous thrombosis.

Results: Primary outcomes (I) and (II) were reduced with treatment compared to placebo (RR 0.41; $P=0.09$ and RR 0.4; $P=0.03$, respectively). There were no differences in overall or cardiovascular mortality and major bleeding episodes.

Conclusion: Low-dose aspirin can safely prevent thrombotic complications in patients with polycythemia vera.



Detection of the *bcr-abl* fusion gene is a diagnostic test for CML (present in over 90% of patients).

Clinical Features

- 3 clinical phases
 - **chronic phase** – disease process easily controlled (85% diagnosed here)
 - ♦ few blasts (<5%) in peripheral film
 - ♦ slightly elevated eosinophils and basophils
 - ♦ no significant symptoms
 - **accelerated phase** – impaired neutrophil differentiation, difficult to control
 - ♦ circulating blasts (10-19%) with increasing peripheral basophils (pruritis)
 - ♦ CBC: thrombocytopenia <100, WBC count unresponsive to therapy
 - ♦ cytogenetic evidence of clonal evolution
 - ♦ worsening constitutional symptoms and splenomegaly (extramedullary hematopoiesis)
 - **blast crisis** – more aggressive course, blasts fail to differentiate
 - ♦ blasts (>20%) in peripheral blood or bone marrow
 - ♦ evolution to acute leukemia (1/3 ALL, 2/3 AML)
 - ♦ large foci of blasts in bone marrow, extramedullary blast proliferation
- clinical presentation
 - 20-50% of patients are asymptomatic when diagnosed (incidental lab finding)
 - nonspecific symptoms
 - ♦ fatigue, weight loss, malaise, excessive sweating, fever
 - secondary to splenic involvement
 - ♦ early satiety, LUQ pain/fullness, shoulder tip pain (referred)
 - ♦ splenomegaly (most common physical finding)
 - anemia
 - bleeding – secondary to platelet dysfunction
 - pruritus, PUD – secondary to increased blood histamine
 - leukostasis, priapism, encephalopathy (rare) – secondary to very elevated WBC (rare)

Investigations

- high increase in WBC, decreased/normal RBC, increased/decreased platelets, increased basophils
- peripheral blood film
 - leukoerythroblastic picture (immature red cells and granulocytes present, e.g. myelocytes and normoblasts)
 - presence of different mid-stage progenitor cells differentiates it from AML
- bone marrow
 - myeloid hyperplasia with left shift, increased megakaryocytes, mild fibrosis
- molecular and cytogenetic studies of bone marrow or peripheral blood for Philadelphia chromosome
- abdominal imaging for spleen size (used in Sokal prognostic scoring system)

Treatment

- **symptomatic**
 - allopurinol and antihistamines
- **chronic phase**
 - imatinib mesylate (Gleevec®) – inhibits proliferation and induces apoptosis by inhibiting tyrosine kinase activity in cells positive for *bcr-abl*
 - ♦ clinical success with imatinib (cytogenetic remission) has resulted in fewer patients requiring bone marrow transplantation
 - dasatinib (tyrosine kinase and src “dual inhibitor”) or nilotinib (selective *bcr-abl1* inhibitor) for those who fail imatinib
 - interferon- α – virtually obsolete with advent of tyrosine kinase inhibitors
 - hydroxyurea (for initial stabilization of WBC counts >20)
 - bone marrow transplantation (curative)
- **accelerated phase**
 - Gleevec® 600 mg PO daily
- **blast crisis**
 - Gleevec® up to 800 mg PO daily
- stem cell transplantation may be curative – to be considered in young patients who do not meet therapeutic milestones
- treatment success is monitored based on therapeutic milestones:
 - hematologic – improved WBC and platelet counts, reduced basophils
 - cytogenetic – reversion of bone marrow to Philadelphia-chromosome negativity
 - molecular – reduction/absence of *bcr-abl* transcripts in periphery and marrow

Prognosis

- survival dependent on response
 - those achieving complete cytogenetic response (CCR) on imatinib by 18 months of therapy – 6 year overall survival >90%
 - those who do NOT achieve CCR on imatinib – 6 year overall survival (OS) of 66%
- acute phase (blast crisis – usually within 3-5 years)
 - 2/3 develop a picture similar to AML
 - ♦ unresponsive to remission induction
 - 1/3 develop a picture similar to ALL
 - ♦ remission induction (return to chronic phase) achievable

Imatinib Compared with Interferon and Low-dose Cytarabine for Newly Diagnosed Chronic-phase Chronic Myeloid Leukemia
NEJM 2003; 348:994-1004

Study: Randomized, open-label, multicenter trial.

Patients: 1106 patients with newly diagnosed chronic-phase chronic myeloid leukemia (CML).

Intervention: Imatinib (553 patients) or interferon- α plus low-dose cytarabine (553 patients).

Outcome: Patients were evaluated for hematologic and cytogenetic responses, toxic effects, and rates of progression.

Results: After a median follow-up of 19 months, the estimated rate of a major cytogenetic response (0 to 35% of cells in metaphase positive for the Philadelphia chromosome) at 18 months was 87.1% (95% CI, 84.1 to 90.0) in the imatinib group and 34.7% (95% CI, 29.3 to 40.0) in the group given interferon- α plus cytarabine ($p < 0.001$). The estimated rates of complete cytogenetic response were 76.2% (95% CI, 72.5 to 79.9) and 14.5% (95% CI, 10.5 to 18.5), respectively ($p < 0.001$). At 18 months, the estimated rate of freedom from progression to accelerated-phase or blast-crisis CML was 96.7% in the imatinib group and 91.5% in the combination-therapy group ($p < 0.001$). Imatinib was better tolerated than combination therapy.

Conclusions: In terms of hematologic and cytogenetic responses, tolerability and the likelihood of progression to accelerated-phase or blast-crisis CML, imatinib was superior to interferon- α plus low-dose cytarabine as first-line therapy in newly diagnosed chronic-phase CML.



The Sokal Score is used to calculate prognosis in CML patients, based on four prognostic factors:

1. Age (Years)
2. Spleen Size (cm)
3. % Myeloblasts in peripheral blood
4. Platelets $> 700 \times 10^3/\text{mm}^3$

The first three criteria are continuous variables with progressively worse prognosis at higher values.

Idiopathic Myelofibrosis (IMF)

Definition

- excessive bone marrow fibrosis leading to marrow failure
- characterized by anemia, extramedullary hematopoiesis, leukoerythroblastosis, teardrop red cells in peripheral blood and hepatosplenomegaly

Epidemiology

- rare, median age at presentation is 65

Pathophysiology

- abnormal myeloid precursor postulated to produce dysplastic megakaryocytes that secrete fibroblast growth factors
 - stimulates fibroblasts and stroma to deposit collagen in marrow
- increasing fibrosis causes early release of hematopoietic precursors leading to:
 - leukoerythroblastic blood film (primitive RBC and WBC present in blood)
 - migration of precursors to other sites – extramedullary hematopoiesis (leading to hepatosplenomegaly)

Clinical Features

- anemia (severe fatigue is most common presenting complaint, pallor on exam in >60%)
- weight loss, fever, night sweats → secondary to hypermetabolic state
- splenomegaly (90%) → secondary to extramedullary hematopoiesis; may cause early satiety
- hepatomegaly (70%) → may get portal hypertension
- bone and joint pain → secondary to osteosclerosis, gout
- signs of extramedullary hematopoiesis (depends on organ involved)

Investigations

- CBC: anemia, variable platelets, variable WBC
- biochemistry: increased ALP (liver involvement, bone disease), increased LDH (2° to ineffective hematopoiesis), increased uric acid (increased cell turnover), increased B₁₂ (2° to increased neutrophil mass), increased leukocyte alkaline phosphatase (LAP)
- blood film: leukoerythroblastosis with teardrop RBCs, nucleated RBCs, variable polychromasia, large platelets and megakaryocyte fragments
- bone marrow aspirate: “dry tap” in as many as 50% of patients
- bone marrow biopsy (essential for diagnosis): fibrosis, atypical megakaryocytic hyperplasia, thickening and distortion of the bony trabeculae (osteosclerosis)

Treatment

- allogeneic stem cell transplant is potentially curative
- symptomatic treatment
 - transfusion for anemia
 - erythropoietin – 30-50% of patients respond
 - androgens (e.g. danazol has shown transient response with response rates of <30%)
 - hydroxyurea for splenomegaly, thrombocytosis, leukocytosis, systemic symptoms
 - ♦ alpha interferon (as second line therapy)
 - ♦ splenectomy (as third line therapy; associated with high mortality and morbidity)
 - XRT for symptomatic extramedullary hematopoiesis, symptomatic splenomegaly
 - thalidomide, JAK2 inhibitors, etanercept

Prognosis

- International Prognostic Scoring System (IPSS) for IMF uses 5 factors to determine mean survival:
 - presence of constitutional symptoms; age >65; hemoglobin <100 g/L; leukocyte count >25,000/mm³; circulating blast cells ≥1%
 - based on the calculated score, a patient's IMF is categorized as “low”, “intermediate 1”, “intermediate 2”, or “high” with a mean survival of 135, 95, 48 and 27 months respectively
- risk of transformation to AML (8-10%)

Essential Thrombocythemia (ET)

Definition

- overproduction of platelets in absence of recognizable stimulus
- must rule out secondary thrombocythemia

Epidemiology

- increases with age; F:M = 2:1 but F=M at older age



Myelofibrosis can be either primary (idiopathic) or occur as a transformation of an antecedent PRV or ET.



A “leukoerythroblastic” blood film (RBC and granulocyte precursors) implies bone marrow infiltration with malignancy (e.g. leukemias, solid tumour metastases) or fibrosis (e.g. IMF).



IMF is characterized by a dry BM aspirate and tear drop RBCs.

Diagnosis (WHO Criteria)

- positive criteria:
 - sustained platelet count $>600 \times 10^9/L$
 - bone marrow biopsy – proliferation of megakaryocyte lineage with enlarged, mature megakaryocytes
 - acquired JAK2 mutation
- criteria for exclusion:
 - no evidence of PRV, CML, IMF, MDS
 - no *bcr-abl* fusion gene
 - no evidence of bone marrow collagen or reticulin fibrosis
 - no evidence of reactive thrombocytosis due to inflammation, infection, neoplasm, prior splenectomy

Clinical Features

- often asymptomatic
- vasomotor symptoms (40%)
 - headache (common), dizziness, syncope
 - erythromelalgia (burning pain of hands and feet, dusky colour, usually worse with heat, caused by platelet activation \rightarrow microvascular thrombosis)
- thrombosis (arterial and venous)
- bleeding (often GI; associated with platelets $>1000 \times 10^9/L$)
- constitutional symptoms, splenomegaly
- pregnancy complications; increased risk of spontaneous abortion
- risk of transformation to AML (0.6-5%), myelofibrosis

Investigations

- CBC: increased platelets; may have abnormal platelet aggregation studies
- bone marrow hypercellularity, megakaryocytic hyperplasia, giant megakaryocytes
- increased K , increased PO_4 (2° to release of platelet cytoplasmic contents)
- diagnosis: exclude other myeloproliferative disorders and reactive thrombocytosis

Treatment

- low dose aspirin if previous history of thrombotic event, ≥ 1 cardiovascular risk factors, older or symptomatic
- cytoreductive therapy if thrombosis or thrombotic symptoms: hydroxyurea (HU) (1st line therapy), anagrelide, interferon-alpha, or ^{32}P (age >80 or lifespan <10 years)
- splenectomy not recommended (increased risk of bleeds, thrombosis)

**Etiology of Secondary Thrombocythemia**

Infection
Inflammation (IBD, arthritis)
Malignancy
Hemorrhage
Iron deficiency
Hemolytic anemia
Post splenectomy
Post chemotherapy



There is an asymptomatic "benign" form of essential thrombocythemia with a stable or slowly rising platelet count. Treatment includes observation, ASA, sulfinpyrazone or dipyridamole.

Lymphoid Malignancies

Acute Lymphoblastic Leukemia (ALL)

Definition

- malignant disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow
- WHO subdivides ALL into two types depending on cell of origin
 - B cell – precursor B lymphoblastic leukemia
 - T cell – precursor T lymphoblastic leukemia

Clinical Features

- see *Acute Myeloid Leukemia*, H35 for full list of symptoms
- distinguish ALL from AML based on Table 21
- 75% ALL occurs in children <6 years old; second peak at age 40
- clinical symptoms usually secondary to:
 - **bone marrow failure** – anemia, neutropenia (50% present with fever; also infections of oropharynx, lungs, perianal region), thrombocytopenia
 - **organ infiltration** – tender bones, lymphadenopathy, hepatosplenomegaly, meningeal signs (headache, N/V, visual symptoms; especially in ALL relapse)

Investigations

- CBC: increased leukocytes $>10 \times 10^9/L$ (occurs in 50% of patients); neutropenia, anemia or thrombocytopenia
- may have increased uric acid, K , PO_4 , Ca , LDH
- PT, aPTT, fibrinogen, D-dimers for DIC
- leukemic lymphoblasts lack specific morphological (no granules) or cytochemical features, therefore diagnosis depends on immunophenotyping
- cytogenetics: Philadelphia (Ph) chromosome in $\sim 25\%$ of adult ALL cases
- CXR: patients with ALL may have a mediastinal mass
- LP prior to systemic chemotherapy to assess for CNS involvement

**FAB Classification of ALL**

L1 blast cells small, uniform high N:C ratio
L2 blast cells larger, heterogeneous, lower N:C ratio
L3 vacuolated blasts, basophilic cytoplasm (usually B-ALL)

**Treatment of ALL vs. AML**

1. No proven benefit of maintenance chemotherapy in AML
2. No routine CNS prophylaxis in AML

Treatment

- eliminate abnormal clone:
 1. **Induction** – to induce complete remission (undetectable leukemic blasts, restore normal hematopoiesis)
 - e.g. Dana-Farber regimen – vincristine (Oncovin®), prednisone, methotrexate, lencorin, L-asparaginase, intrathecal methotrexate and ara-c
 - in Philadelphia chromosome-positive ALL, add imatinib mesylate (Gleevec®, a *bcr-abl* tyrosine kinase inhibitor); found to induce complete remission in up to 95% cases
 2. **Consolidation and/or intensification chemotherapy**
 - consolidation – continuing same chemotherapy to eliminate subclinical leukemic cells
 - intensification – high doses of different (non-cross-reactive) chemotherapy drugs to eliminate cells with resistance to primary treatment
 3. **Maintenance chemotherapy** – low dose intermittent chemotherapy over prolonged period (2-3 years) to prevent relapse
 4. **Prophylaxis:** CNS radiation therapy or methotrexate (intrathecal or systemic)
- hematopoietic stem cell transplantation – potentially curative (due to pre-implant myeloablative chemoradiation and post-implant graft-versus-leukemia effect) but relapse rates and non-relapse mortality high

Prognosis

- depends on response to initial induction or if remission is achieved following relapse
- good prognostic factors: young, WBC <30 x 10⁹/L, T-cell phenotype, absence of Ph chromosome, early attainment of complete remission
- achievement of first remission: 60-90%
- childhood ALL: 80% long term remission (>5 years)
 - higher cure rates in children because of better chemotherapy tolerance, lower prevalence of *bcr-abl* fusion gene (associated with chemotherapeutic resistance)
- adult ALL: 30-40% 5-year survival

Table 21. Differentiate AML From ALL

AML	ALL
Big people (adults)	Small people (kids)
Big blasts	Small blasts
Big mortality rate	Small mortality rate
Lots of cytoplasm	Less cytoplasm
Lots of nucleoli (3-5)	Few nucleoli (1-3)
Lots of granules and Auer rods	No granules
Myeloperoxidase, Sudan black stain	PAS (periodic acid schiff)
Maturation defect beyond myeloblast or promyelocyte	Maturation defect beyond lymphoblast



To Differentiate AML From ALL:
Remember **Big** and **SmALL**
(see Table 21)

Lymphomas

Definition

- collection of lymphoid malignancies in which malignant lymphocytes accumulate at lymph nodes and lymphoid tissues
 - leading to lymphadenopathy, extranodal disease and constitutional symptoms

Staging (Ann Arbor Staging System)

- Stage I
 - involvement of a single lymph node region or extralymphatic organ or site
- Stage II
 - involvement of two or more lymph node regions or an extralymphatic site and one or more lymph node regions on same side of diaphragm
- Stage III
 - involvement of lymph node regions on both sides of the diaphragm; may or may not be accompanied by single extra lymphatic site or splenic involvement
- Stage IV
 - diffuse involvement of one or more extralymphatic organs including bone marrow
- subtypes:
 - A = absence of B symptoms
 - B = presence of B symptoms
 - ♦ unexplained fever >38°C
 - ♦ unexplained weight loss (>10% of body weight in 6 months)
 - ♦ night sweats



- Ann Arbor staging can be used for both Hodgkin's and non-Hodgkin's lymphoma, but grade/histology is more important for non-Hodgkin's lymphoma because the outcome differs significantly depending on type of lymphoma.
- Prognostic scores are different for indolent versus aggressive lymphomas.
- Highly aggressive lymphomas act like acute leukemias.



Hodgkin's is distinguished from non-Hodgkin's lymphoma by the presence of Reed-Sternberg cells.

Table 22. Chromosome Translocations

Translocation	Gene Activation	Associated Neoplasm
t(8;14)	c-myc activation	Burkitt's lymphoma
t(14;18)	bcl-2 activation	Follicular lymphoma
t(9;22)	Philadelphia chromosome (<i>bcr-abl</i> hybrid)	CML, ALL in adults (25% of the time)
t(11;14)	Overexpression protein cyclin D1	Mantle cell lymphoma

Hodgkin's Lymphoma

Definition

- malignant proliferation of lymphoid cells with Reed-Sternberg cells (thought to arise from germinal centre B-cells)

Epidemiology

- bimodal distribution with peaks at 20 years and >50 years
- association with Epstein-Barr virus in up to 50% of cases

Clinical Features

- asymptomatic lymphadenopathy (70%)
 - non-tender, rubbery consistency
 - cervical/supraclavicular (60-80%), axillary (10-20%), inguinal (6-12%)
- splenomegaly (50%) ± hepatomegaly
- mediastinal mass
 - found on routine CXR, may be symptomatic (cough)
 - rarely may present with SVC syndrome, pleural effusion
- systemic symptoms
 - B symptoms (especially in widespread disease; fever in 30%), pruritus
- non-specific/paraneoplastic
 - alcohol-induced pain in nodes, nephrotic syndrome
- starts at a single site in lymphatic system (node), spreads first to adjacent nodes
 - disease progresses in contiguity with lymphatic system

Investigations

- CBC
 - anemia (chronic disease, rarely hemolytic), eosinophilia, leukocytosis, platelets normal or increased early, decreased in advanced disease
- biochemistry
 - LFTs (liver involvement)
 - RFTs (prior to initiating chemotherapy)
 - ALP, Ca (bone involvement)
 - ESR, LDH (monitor disease progression)
- imaging
 - CXR, CT chest (lymph nodes, mediastinal mass), CT abdomen/pelvis (liver or spleen involvement), gallium scan (assess treatment response)
 - cardiac function assessment – (MUGA or echocardiography) for patients at high risk of pre-treatment cardiac disease (age >60, history of HTN, CHF, PUD, CAD, MI, CVA)
 - PFTs – if history of lung disease (COPD, smoking, previous radiation to lung)
- excisional lymph node biopsy confirms diagnosis
- bone marrow biopsy to assess marrow infiltration (only necessary if B symptoms, stage III or IV, bulky disease or cytopenia)

Treatment

- stage I-II: chemotherapy (ABVD) followed by involved field radiotherapy (XRT)
- stage III-IV: chemotherapy (ABVD, BEACOPP) with XRT for bulky disease
- relapse, resistant to therapy: high dose chemotherapy, bone marrow transplant
 - PET scans used to follow response to treatment

Complications of Treatment

- cardiac disease – secondary to XRT (adriamycin is cardiotoxic)
- pulmonary disease – secondary to bleomycin (interstitial pneumonitis)
- infertility – recommend sperm banking
- secondary malignancy in irradiated field
 - <2% risk of MDS, AML (secondary to treatment, usually within 8 years)
 - solid tumours of lung, breast; >10 years after treatment
 - non-Hodgkin's lymphoma
- hypothyroidism – post XRT



Hodgkin's Lymphoma classically presents as a painless, non-tender, firm, rubbery enlargement of superficial lymph nodes, most often in the cervical region.



CHOP = cyclophosphamide, hydroxydoxorubicin (Adriamycin), vincristine (Oncovin), prednisone

VAD = vincristine, adriamycin, dexamethasone

ABVD = adriamycin, bleomycin, vinblastine, dacarbazine

BEACOPP = bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone



International Prognostic Factors Project 1998

Prognostic Factors FFP

0	84%
1	77%
2	67%
3	60%
4	51%
5-7	42%

FFP = freedom from progression at 5 years.

Prognosis

- adverse prognostic factors:
 - serum albumin <40 g/L (4 g/dL)
 - hemoglobin <105 g/L (10.5 g/dL)
 - male
 - stage IV disease
 - age ≥45 years
 - leukocytosis (WBC >1.5 × 10⁹/L)
 - lymphocytopenia (lymphocytes <0.06 × 10⁹/L or <8% of WBC count or both)
- prognostic score
 - each additional adverse prognostic factor decreases freedom from progression at 5 years

Non-Hodgkin's Lymphoma (NHL)

Definition

- malignant proliferation of lymphoid cells of progenitor or mature B or T cells

Classification

- multiple classification systems exist at present and may be used at different centres
- can originate from both B- (85%) and T- or NK- (15%) cells
 - B cell NHL – e.g. Burkitt's lymphoma, mantle cell lymphoma, follicular lymphoma
 - T cell NHL – e.g. mycosis fungoides, anaplastic large cell lymphoma
- WHO/REAL classification system – 3 categories of NHLs based on natural history
 - indolent** (35-40% of NHL) – e.g. follicular lymphoma, small lymphocytic lymphoma/CLL, mantle cell lymphoma
 - aggressive** (~50% of NHL) – e.g. diffuse large B-cell lymphoma
 - highly aggressive** (~5% of NHL) – e.g. Burkitt's lymphoma

Clinical Features

- painless superficial lymphadenopathy, usually >1 lymph node region
- usually presents as widespread disease (exception is aggressive lymphoma)
- constitutional symptoms not as common as in Hodgkin's disease
- cytopenia: anemia ± neutropenia ± thrombocytopenia can occur when bone marrow is involved
- abdominal signs
 - hepatosplenomegaly
 - retroperitoneal and mesenteric involvement (2nd most common site of involvement)
- oropharyngeal involvement in 5-10% with sore throat and obstructive apnea
- extranodal involvement – most commonly GI tract; also testes, bone, kidney
- CNS involvement in 1% (often with HIV)

Investigations

- CBC
 - normocytic normochromic anemia
 - autoimmune hemolytic anemia
 - advanced disease: thrombocytopenia, neutropenia and leukoerythroblastic anemia
- peripheral blood film may show lymphoma cells
- biochemistry
 - increase in uric acid
 - abnormal LFTs in liver metastases
 - increased LDH (rapidly progressing disease, poor prognostic factor)
- CXR, CT chest, abdomen, pelvis for staging
- gallium scan is useful for monitoring response to treatment and evaluation of residual tumour following therapy in aggressive histological disease
- diagnosed by
 - lymph node biopsy – excisional biopsy preferred, FNA unreliable
 - bone marrow biopsy – not optimal for diagnosis as BM may not be involved

Treatment

- localized disease (e.g. GI, brain, bone, head and neck)
 - radiotherapy to primary site and adjacent nodal areas
 - adjuvant chemotherapy
 - surgery: splenic marginal zone lymphoma
- indolent lymphoma** – goal of treatment is symptom management
 - watchful waiting
 - radiation therapy for localized disease
 - chemotherapy for advanced stage disease [single agent or combination with rituximab (Rituxan®), an anti-CD20 antibody]



NHL: Associated Conditions

- Immunodeficiency (e.g. HIV)
- Autoimmune diseases (e.g. SLE)
- Infections (e.g. EBV)

CHOP-like Chemotherapy Plus Rituximab versus CHOP-like Chemotherapy Alone in Patients with Diffuse Large-B-cell Lymphoma (MINT)

Lancet Oncol 2006; 7:379-91

Study: Randomized controlled trial with a median follow-up of 34 months.

Participants: 824 patients with good-prognosis diffuse large-B-cell lymphoma who had ≤1 risk factor, stage II-IV disease or stage I disease with bulk (age: 18 to 60 years).

Intervention: Patients received either 6 cycles of CHOP-like chemotherapy and rituximab (CCR; n=413) or 6 cycles of CHOP-like chemotherapy alone (CLC; n=411). Bulky and extranodal sites received additional radiotherapy.

Primary Outcome: Event-free survival. Secondary outcomes included: response, progression under therapy, progression-free survival, overall survival and frequency of toxic effects.

Results: Patients receiving CCR had an increased 3-year event-free survival compared with the CLC group (79% vs. 59%; P<0.0001) and an increased 3-year overall survival (93% vs. 84%; P=0.0001). Frequency of adverse events did not differ between groups.

Conclusion: Rituximab added to six cycles of CHOP is an effective treatment for young patients with good-prognosis diffuse large-B-cell lymphoma.

- **aggressive lymphoma** – goal of treatment is curative
 - combination chemotherapy: CHOP is mainstay, plus rituximab if B-cell lymphoma
 - radiation for localized/bulky disease
 - CNS prophylaxis with high-dose methotrexate if certain sites involved
 - relapse, resistant to therapy: high dose chemotherapy, BMT
- **highly aggressive lymphoma**
 - Burkitt's Lymphoma – short bursts of intensive chemotherapy
 - “CODOX-M” chemotherapy regimen also often used \pm IVAC
 - CNS prophylaxis and tumour lysis syndrome prophylaxis



Treatment of HL depends on stage; treatment of NHL depends on histologic subtype.

Complications

- hypersplenism
- infection
- autoimmune hemolytic anemia and thrombocytopenia
- vascular obstruction (from enlarged nodes)
- tumour lysis syndrome (particularly in very aggressive lymphoma) – see H50

Prognosis

- follicular lymphoma – Follicular Lymphoma International Prognostic Index is used (5 adverse prognostic factors): age >60 ; number of nodal areas >4 ; elevated LDH; Ann Arbor stage III-IV; hemoglobin <120 g/L
 - based on calculated risk, mean 5 year survival ranges from 53-91%
- diffuse large B-cell lymphoma – The International Prognostic Factor Index is used (5 adverse prognostic factors): age >60 ; Ann Arbor stage (III-IV); performance status (ECOG/Zubrand 2-4); elevated LDH; >1 extranodal site
 - based on calculated risk, mean 5 year survival ranges from 26-73%

Table 23. Characteristics of Selected Non-Hodgkin's Lymphomas

	Follicular Lymphoma	Diffuse Large B-Cell Lymphoma (DLBCL)	Burkitt's Lymphoma	Mantle Cell Lymphoma
Percentage of NHLs	22-30%	33%	$<1\%$ adult NHLs 30% childhood NHLs	6%
Genetic Mutation	Bcl-2 activation	Bcl-2, Bcl-6, MYC rearrangements	c-myc activation	Overexpression of cyclin D1 (Bcl-1 activation)
Classification	Indolent	Aggressive (high-grade)	Very aggressive	Indolent
Risk Factors	Middle-age – elderly	Previous CLL (Richter's transf.: 5% CLL patients progress to DLBCL)	1. Endemic – African origin, EBV-associated 2. Sporadic – no EBV 3. HIV-related – AIDS-defining illness	Male (male:female = 4:1)
Clinical Features	<ul style="list-style-type: none"> • Widespread painless LAD* \pm bone marrow involvement • Frequent transformation to aggressive lymphoma • Very responsive to chemoradiation tx 	<ul style="list-style-type: none"> • Rapidly progressive LAD and extranodal infiltration • 50% present at stage I/II, 50% widely disseminated 	<ul style="list-style-type: none"> • Endemic form – massive jaw LAD • “Starry-sky” histology • High risk of tumour lysis syndrome upon treatment 	<ul style="list-style-type: none"> • Often presents Stage IV with palpable LAD • Involvement of GI tract (lymphomatous polyposis), Waldeyer's Ring • Extremely aggressive, 5-year survival 25%

*LAD = lymphadenopathy

Malignant Clonal Proliferations of Mature B Cells

Table 24. Characteristics of B-Cell Malignant Proliferation

	CLL	Macroglobulinemia	Myeloma
Cell Type	Lymphocyte	Plasmacytoid	Plasma cell
Protein	IgM if present	IgM	IgG, A, light chain, M, D or E
Lymph Nodes	Very common	Common	Rare
Hepatosplenomegaly	Common	Common	Rare
Bone Lesions	Rare	Rare	Common
Hypercalcemia	Rare	Rare	Common
Renal Failure	Rare	Rare	Common
Immunoglobulin Complications	Common	Infrequent	Rare



Rouleaux formation on peripheral blood smear, if not artifact, denotes hyperglobulinemia (but not necessarily monoclonality).



Chronic Lymphocytic Leukemia (CLL)

Definition

- indolent disease characterized by clonal malignancy of mature B-cells

Epidemiology

- most common leukemia in Western world
- mainly older patients; median age 65 years
- M>F

Pathophysiology

- accumulation of neoplastic lymphocytes in blood, bone marrow, lymph nodes and spleen

Clinical Features

- 25% asymptomatic (incidental finding)
- 5-10% present with B symptoms (≥ 1 of: unintentional weight loss $\geq 10\%$ of body weight within previous 6 months, fevers $>38^\circ\text{C}$ or night sweats for ≥ 2 weeks without evidence of infection, extreme fatigue)
- lymphadenopathy (50-90%), splenomegaly (25-55%), hepatomegaly (15-25%)
- immune dysregulation – autoimmune hemolytic anemia (Coombs positive), immune thrombocytopenic purpura (ITP), hypogammaglobulinemia \pm neutropenia
- bone marrow failure – late, secondary to marrow involvement by CLL cells

Investigations

- CBC: absolute lymphocytosis $>5 \times 10^9/\text{L}$
- peripheral blood film
 - lymphocytes are small and mature
 - smudge cells
- flow cytometry
- cytogenetics – FISH
- bone marrow aspirate
 - lymphocytes $>30\%$ of all nucleated cells
 - infiltration of marrow by lymphocytes in 3 patterns: nodular (10%), interstitial (30%), diffuse (35%, worse prognosis) or mixed (25%)

Natural History and Treatment

- natural history – indolent but incurable, with slow progression; thus select gentlest treatment that will control symptoms
 - observation if early, stable, asymptomatic
 - intermittent chlorambucil or fludarabine chemotherapy combined with Rituximab
 - corticosteroids, IVIG – especially for autoimmune phenomena
 - radiotherapy
- small minority present with aggressive disease; usually associated with chromosomal abnormalities (e.g. p53 deletion)
- 9 year median survival, but varies greatly



Smudge cells are artifacts of damaged lymphocytes from slide preparation.

- prognosis predicted by Rai staging
 - low risk: lymphocytosis in blood and bone marrow only
 - intermediate risk: lymphocytosis with enlarged nodes in any site or splenomegaly, hepatomegaly
 - high risk: lymphocytosis with disease-related anemia (<110 g/L) or thrombocytopenia ($<100 \times 10^9/L$)

Complications

- bone marrow failure
- immune complications – autoimmune hemolytic anemia, immune thrombocytopenic (ITP), immune deficiency (hypogammaglobulinemia, impaired T-cell function)
- polyclonal or monoclonal gammopathy (often IgM)
- hyperuricemia with treatment
- 5% undergo **Richter's Transformation** – aggressive transformation to Diffuse Large B-Cell Lymphoma (see Table 23)

Multiple Myeloma (MM)



Definition

- neoplastic proliferation of a clone of plasma cells producing a monoclonal immunoglobulin
- usually single clone of plasma cells, although biclonal myeloma also occurs

Epidemiology

- incidence 3 per 100,000, most common plasma cell malignancy
- increased frequency with age; median age of diagnosis is 68; M>F

Pathophysiology

- malignant plasma cells secrete monoclonal antibody
 - 95% produce M protein (monoclonal Ig = identical heavy chain + identical light chain, or light chains only)
 - ♦ IgG 50%, IgA 20%, IgD 2%, IgM 0.5%
 - ♦ 15-20% produce free light chains or light chains alone found in either:
 - serum as an increase in the quantity of either kappa or lambda light chain (with an abnormal kappa:lambda ratio)
 - urine as Bence-Jones Protein
 - <5% are non-secretors

Clinical Features and Complications

- bone disease – pain (usually back), bony tenderness, pathologic fractures
 - lytic lesions are classical (skull, spine, proximal long bones, ribs)
 - increased bone resorption secondary to osteoclast activating factors such as PTHrP
- anemia – weakness, fatigue, pallor
 - secondary to bone marrow suppression
- weight loss
- infections
 - usually *S. pneumoniae* and Gram-negatives
 - secondary to suppression of normal plasma cell function
- hypercalcemia – N/V, confusion, constipation, polyuria, polydipsia
 - secondary to increased bone turnover
- renal disease/renal failure
 - most frequently causes cast nephropathy (see Nephrology, NP34)
- bleeding
 - secondary to thrombocytopenia, may see petechiae, purpura
 - can also be caused by acquired von Willebrand disease
- extramedullary plasmacytoma
 - soft tissue mass composed of monoclonal plasma cells, purplish colour
- hyperviscosity – may manifest as headaches, stroke, angina, MI
 - secondary to increased viscosity caused by M protein
- amyloidosis
 - accumulation of insoluble fibrillar protein (Ig light chain) in tissues; can cause infiltration of any organ system: cardiac infiltration – diastolic dysfunction, cardiac arrhythmias, syncope, sudden death; GI involvement – malabsorption, beefy large or laterally scalloped tongue; neurologic involvement – orthostatic hypotension, carpal tunnel syndrome
 - may cause Factor X deficiency if fibrils bind Factor X → bleeding (raccoon eyes)
- neurologic disease – muscle weakness, pain, paresthesias
 - radiculopathy caused by vertebral fracture, extramedullary plasmacytoma
 - spinal cord compression (10-20% of pts) is a medical emergency



Multiple Myeloma

CRAB

Increased Calcium

Renal failure

Anemia

Bony lesions (lytic or osteoporosis felt to be caused by myeloma)



Routine urinalysis will not detect light chains as dipstick detects albumin. Need sulfosalicylic acid or 24 hour urine protein for immunofixation or electrophoresis.



Diagnosis of MM (WHO)

Major Criteria

1. Bone marrow >30% plasma cells
2. Plasmacytoma on tissue biopsy
3. High paraproteins (elevated serum IgG, IgA or light chain excretion)

Minor Criteria

1. Bone marrow plasmacytosis 10-30%
2. Monoclonal protein less than major criteria levels
3. Lytic bone lesions
4. Reduced non-clonal Ig levels



Amyloid

The general term for a variety of proteinaceous materials that have a similar structural organization and are abnormally deposited in tissues.

Found in a variety of clinical disorders and can cause systemic [e.g. MM (light chains)] or localized amyloidosis [e.g. Alzheimer disease (AB amyloid)].

Melphalan and Prednisone ± Thalidomide versus Melphalan and Reduced-intensity Autologous Stem Cell Transplantation in Elderly Patients with Multiple Myeloma
Lancet 2007; 370:1209-18

Study: Randomized control trial with a median follow up of 51.1 months.

Participants: 447 previously untreated patients with multiple myeloma (age 65 to 75 years).

Intervention: Patients received either melphalan plus prednisone (MP; n=196), MP plus thalidomide (MPT; n=125) or reduced-intensity stem cell transplantation using melphalan 100 mg/m² (MEL100; n=126).

Primary Outcome: Survival rate

Results: Median survival rates were 33.2 months (13.8-54.8) for MP, 51.6 months (26.6-not reached) for MPT, and 38.3 months (13.0-61.6) for MEL100. Survival was significantly higher with the MPT therapy than MP (HR 0.59; P=0.0006) or MEL100 (0.69; P=0.027).

Conclusion: Thalidomide in combination with melphalan and prednisone is more efficacious for previously untreated elderly patients with multiple myeloma.



Light Chain Disease

15% of MM produce only light chains. Renal failure is a major problem. Kappa > lambda light chain better prognosis.

Investigations

- CBC
 - normocytic anemia, thrombocytopenia, leukopenia
 - rouleaux formation on peripheral film
- biochemistry
 - increased Ca, increased ESR, decreased anion gap, increased Cr, albumin, beta2-microglobulin (as part of staging), proteinuria (24 hour urine collection)
- monoclonal proteins
 - serum protein electrophoresis (SPEP) – demonstrates monoclonal protein spike in serum in 80% (i.e. M protein)
 - urine protein electrophoresis (UPEP) – demonstrates light chains in urine = Bence-Jones Protein (15% only secrete light chains)
 - immunofixation – demonstrates M protein and identifies Ig type; also identifies light chains
 - serum free light chain quantification – kappa and lambda light chains, calculated ratio
- bone marrow aspirate and biopsy
 - often focal abnormality, greater than 10% plasma cells, abnormal morphology, clonal plasma cells; send for FISH or cytogenetics (prognostic implications)
- skeletal series (x-rays), MRI if symptoms of cord compression
 - presence of lytic lesions and areas at risk of pathologic fracture
 - bone scans are not useful since they detect osteoblast activity
- beta-2 microglobulin, LDH and CRP are poor prognosticators

Diagnosis

- International Myeloma working group criteria
 1. serum or urinary monoclonal protein
 2. presence of clonal plasma cells in bone marrow or a plasmacytoma
 3. presence of end-organ damage related to plasma cell dyscrasia, such as:
 - ♦ increased serum Ca
 - ♦ lytic bone lesions
 - ♦ anemia
 - ♦ renal failure

Treatment

- treatment is non-curative
- treatment goals:
 - improvement in quality of life (improve anemia, reverse renal failure, bony pains)
 - prevention of progression and complications
 - increase overall survival
- autologous stem cell transplant if <70 years old
 - usually preceded by 4-6 months of cytoreductive therapy utilizing a regimen that includes steroids (prednisone or dexamethasone)
- chemotherapy if >70 years old or transplant-ineligible
 - consider melphalan and prednisone alone if >75 years old
 - melphalan, prednisone and thalidomide or melphalan, prednisone and bortezomib if 65-75 years
- dexamethasone and bortezomib if ARF; bortezomib ± dexamethasone in light chain amyloidosis
- supportive management:
 - bisphosphonates for those with osteoporosis or lytic bone lesions
 - local XRT for bone pain, spinal cord compression
 - kyphoplasty for vertebral fractures to improve pain relief and regain height
 - treat complications: hydration for hypercalcemia and renal failure, bisphosphonates for severe hypercalcemia, prophylactic antibiotics, erythropoietin for anemia
- all patients will relapse; choice of retreatment regimen depends on duration of remission, organ involvement, patient's comorbidities and preferences

Prognosis

- Salmon-Durie (Hb, calcium, M protein, radiograph appearance and creatinine) and International Staging System (beta-2 micoglobulin, CRP, chromosome 13 status, serum IL-6, duration of initial plateau phase) used to stage and estimate prognosis
- median survival based on stage usually 16-70 months

Monoclonal Gammopathy of Unknown Significance (MGUS)

Definition

- presence of M protein in serum in absence of any clinical or laboratory evidence of a plasma cell dyscrasia or lymphoproliferative disorders
 - incidence: 0.15% in general population, 5% of people >70 years of age
 - asymptomatic

Diagnosis

- presence of a serum monoclonal protein (M-protein) at a concentration <30 g/L
- <10% plasma cells in bone marrow
- absence of hyperCalcemia, Renal insufficiency, Anemia, Bony disease related to the plasma cell proliferative process (absence of "CRAB")
- 0.3-1% of patients develop a hematologic malignancy each year
 - patients with M protein peak ≥ 15 g/L or patients with IgA or IgM MGUS are at higher risk of malignant transformation
 - patients with serum free light chains are at increased risk of malignant transformation
- monitor with annual history, physical, CBC, Cr, calcium, albumin, serum protein electrophoresis (considered pre-malignant)

Waldenstrom's Macroglobulinemia

Definition

- proliferation of lymphoplasmacytoid cells
 - presence of monoclonal IgM paraprotein

Clinical Features

- chronic disorder of elderly patients; median age 64
- symptoms: weakness, fatigue, bleeding (oronasal), weight loss, recurrent infections, dyspnea, CHF (triad of anemia, hyperviscosity, plasma volume expansion), neurological symptoms, peripheral neuropathy, cerebral dysfunction
- signs: pallor, splenomegaly, hepatomegaly, lymphadenopathy, retinal lesions
- key complication to avoid: Hyperviscosity Syndrome (see below)
 - because IgM (unlike IgG) confined largely to intravascular space

Investigations and Diagnosis

- bone marrow shows plasmacytoid lymphocytes
- bone lesions usually not present
- bloodwork – rarely see hypercalcemia
- cold hemagglutinin disease possible – Raynaud's phenomenon, hemolytic anemia precipitated by cold weather
- normocytic anemia, rouleaux, high ESR if hyperviscosity not present

Management

- alkylating agents (chlorambucil), nucleoside analogues (fludarabine), thalidomide, rituximab, or combination therapy
- corticosteroids
- plasmapheresis for hyperviscosity – acute reduction in serum IgM

Serum Free Light Chain Ratio is an Independent Risk Factor for Progression in Monoclonal Gammopathy of Undetermined Significance (MGUS)

Blood 2005; 106:812-7.

Study: A retrospective study determining whether the presence of monoclonal free kappa or lambda immunoglobulin light chains in monoclonal gammopathy of undetermined significance (MGUS), increases the risk of progression to malignancy.

Methods: Baseline serum samples obtained from 1383 MGUS patients seen at the Mayo clinic between 1960-1994. 1148 baseline samples were obtained within 30 days of diagnosis.

Results: Malignant progression had occurred in 87 (7.6%) patients at a median follow-up of 15 years. In 379 (33%) patients an abnormal serum free light chain (FLC) ratio was detected. There was a significantly higher risk of progression in patients with an abnormal FLC ratio relative to patients with a normal ratio (hazard ratio, 3.5; 95% CI, 2.3-5.5; $p < 0.001$). This finding was independent of the size and type of the serum monoclonal (M) protein.

Conclusions: In high-risk MGUS patients (abnormal serum FLC ratio, non-IgG MGUS, high serum M protein level (≥ 1.5 gm/dL)) the risk of progression at 20 years was 58% compared to 37% in high-intermediate-risk MGUS (two risk factors), 21% low-intermediate risk (with one risk factor) and 5% low-risk (no risk factors).



Waldenstrom's macroglobulinemia accounts for 85% of all cases of hyperviscosity syndrome.

Complications of Hematologic Malignancies

Hyperviscosity Syndrome

Definition

- refers to clinical sequelae of increased blood viscosity (when relative serum viscosity >5-6), resulting from increased circulating serum Igs or from increased cellular blood components in hyperproliferative disorders (e.g. multiple myeloma, leukemia, PV)
- Waldenstrom's macroglobulinemia accounts for 85% of cases

Clinical Features

- hypervolemia causing: CHF, headache, lethargy, dilutional anemia
- CNS symptoms due to decreased cerebral blood flow: headache, vertigo, ataxia, stroke
- retina shows venous engorgement and hemorrhages
- bleeding diathesis
 - due to impaired platelet function, absorption of soluble coagulation factors (e.g. nasal bleeding, oozing gums)
- ESR usually very low

Treatment

- plasmapheresis

Tumour Lysis Syndrome

Definition

- group of metabolic complications that result from spontaneous or treatment-related breakdown of cancer cells
- more common in diseases with large tumour burden and high proliferative rate (high grade lymphoma, leukemia)

Clinical Features

- metabolic abnormalities
 - cells lyse, releasing K, uric acid, PO_4 (increased levels)
 - PO_4 binds Ca (decreased Ca)
- complications
 - lethal cardiac arrhythmia (increased K)
 - acute renal failure (urate nephropathy)

Treatment

- prevention
 - aggressive IV hydration
 - alkalinization of the urine
 - allopurinol
 - correction of pre-existing metabolic abnormalities
- dialysis

Blood Products and Transfusions

Blood Products

- RBCs, platelets and coagulation factors (fresh frozen plasma, cryoprecipitate, factor concentrates) are available for transfusion
- donated blood (1 U = 450-500 mL) is fractionated into these various components
 - centrifugation separates whole blood into RBCs and platelet-rich plasma
 - platelet rich plasma is further fractionated into platelets and plasma
 - ♦ need to pool together multiple units to obtain therapeutic amounts
 - ♦ FFP is plasma frozen within 8 hours of collection
 - ♦ cryoprecipitate is the high MW precipitate generated when FFP is thawed at low temperatures

Specialized Products

- irradiated blood products
 - prevent proliferation of donor T-cells in potential or actual BMT recipients
 - used for immunocompromised patients
- CMV-negative blood products
 - potential transplant recipients
 - neonates
 - AIDS patients
 - seronegative pregnant women

**Blood Groups**

Group	Antigen	Antibody
O	H	Anti-A, anti-B
A	A	Anti-B
B	B	Anti-A
AB	A and B	Nil



In Canada, blood products are leukodepleted via filtration immediately after donation. Therefore it is considered:

- Low in lymphokines, resulting in a lower incidence of febrile nonhemolytic transfusion reactions
- CMV negative (because CMV found in leukocytes)

Red Blood Cells

Packed Red Blood Cells

- stored at 4°C
- transfuse within 35 days of collection, otherwise cell lysis may result in hyperkalemia
- transfuse within 7 days of collection if renal failure or hepatic failure is present to reduce solute load
- infuse each unit over 2 hours, max of 4 hours

Indications for pRBC Transfusion

- Hb <70 g/L (7 g/dL)
 - maintain Hb between 70 and 100 g/L during active bleeds (7 g/dL to 10 g/dL)
- consider maintaining a higher Hb for patients with:
 - CAD/unstable coronary syndromes
 - uncontrolled, unpredictable bleeding
 - impaired pulmonary function
 - increased O₂ consumption

Frozen Red Blood Cells

- used for recipients with rare blood groups or multiple auto-antibodies

Selection of Red Cells for Transfusion

- when a need for RBC transfusion is anticipated, the following should be ordered:
 - group and screen
 - ♦ determines the blood group and Rh status of the recipient as well as the presence of autoantibodies vs. major/minor blood group antigens
 - crossmatch
 - ♦ involves mixing the recipient's blood with potential donor blood and looking for clotting
 - ♦ takes 30–45 min
- when blood is required, several options are available
 - 1st line: fully crossmatched blood (not always available in emergency situations)
 - 2nd line: donor blood of the same group and Rh status as the recipient
 - 3rd line: O- blood for females of reproductive age; O+ blood for all others



1 unit of pRBC will approximately increase Hb by 10 g/L or increase Hct by 4%.

Transfusion Requirements in Critical Care (TRICC)

NEJM 1999; 340:409-17

Study: Multicentre, randomized control trial.

Participants: 838 critically ill patients with euvoolemia after initial treatment and hemoglobin less than 9 g/dL within 72 hours of ICU admission.

Intervention: Patients receiving a transfusion followed either (1) a restrictive strategy (RS; n=418) in which red cells were transfused if hemoglobin was less than 7.0 g/dL and then maintained at 7 to 9 g/dL or (2) a liberal strategy (LS; n=420) in which transfusions occurred when the hemoglobin was less than 10.0 g/dL and then maintained at 10 to 12 g/dL.

Primary Outcome: Mortality at 30 days and severity of organ dysfunction.

Results: Mortality rates at 30 days were similar between groups. However, mortality rates were significantly lower with the RS among less acutely ill patients (8.7% and RS group and 16.1% in LS group; P=0.03) and among those less than 55 years of age (5.7% RS and 13% LS; P=0.02), but did not differ in a subgroup with clinically significant cardiac disease.

Conclusion: A RS of red cell transfusion is at least as effective as, and possibly superior to, a LS transfusion in critically ill patients. Transfusion strategies in patients with acute myocardial infarction and unstable angina need further study.

Platelets

Table 25. Platelet Products

Product	Indication
Random donor (pooled)	Thrombocytopenia with bleeding
Single donor platelets	Potential BMT recipients
HLA matched platelets	Refractory to pooled or single donor platelets

- stored at 20–24°C
- random donor platelets are transfused in groups of 5 units; this should increase the platelet count by at least $15 \times 10^9/L$
- single donor platelets (transfused as single units) should increase the platelet count by $40-60 \times 10^9/L$
- if an increase in the platelet count is not seen post-transfusion: alloantibodies, bleeding, sepsis or hypersplenism may be present

Table 26. Indications for Platelet Transfusion

Plt ($\times 10^9/L$)	Indications
<10	Non-immune thrombocytopenia
<20	Procedures not associated with significant blood loss
<50	Procedures associated with blood loss or major surgery (>500 mL EBL)
<100	Pre-neurosurgery or head trauma
Any	Platelet dysfunction and marked bleeding

Relative Contra-indications of Platelet Transfusion

- TTP, HIT, post-transfusion purpura, HELLP

Coagulation Factors

Table 27. Coagulation Factor Products

Product	Indication
Fresh Frozen Plasma (FFP)	Depletion of multiple coagulation factors (e.g. sepsis, DIC, dilution, TTP/HUS, liver disease), emergency reversal of life-threatening bleeding secondary to warfarin overdose
Cryoprecipitate (enriched fibrinogen, vWF, VIII, XIII)	Factor VIII deficiency von Willebrand's disease Hypofibrinogenemia
Hemate P	von Willebrand's disease
Factor VIII concentrate	Factor VIII deficiency (Hemophilia A)
Factor IX concentrate	Factor IX deficiency (Hemophilia B)
Recombinant VIIa	Factor VII deficiency, CNS bleeds, severe trauma, Hemophilia A or B with inhibitors
Prothrombin Complex (Octaplex®)	Reversal of warfarin therapy or vitamin K deficiency in bleeding patient or in patient requiring urgent (<6 hours) surgical procedure

Acute Blood Transfusion Reactions

IMMUNE

Acute Hemolytic Transfusion Reactions (AHTR)

- ABO incompatibility resulting in intravascular hemolysis secondary to complement activation
- most commonly due to incorrect patient identification
- occurs immediately after transfusion
- risk per unit of blood is <1 in 250,000
- presents with fever, chills, hypotension, back or flank pain, dyspnea, hemoglobinuria
- acute renal failure (<24 hrs) and DIC
- treatment
 - stop transfusion
 - notify blood bank and check for clerical error
 - maintain BP with vigorous IV fluids ± inotropes
 - maintain urine output with diuretics, crystalloids, dopamine

Febrile Nonhemolytic Transfusion Reactions (FNHTR)

- due to alloantibodies to WBC, platelets or other donor plasma antigens and release of cytokines from blood product cells
- occurs within 0-6 hours of transfusion
- risk per unit of blood is 1 in 100 (minor), 1 in 10,000 to 40,000 (severe)
- presents with fever ± rigors, facial flushing, headache, myalgia, hypotension
- treatment
 - rule out hemolytic reaction or infection
 - if fever <38°C, continue with transfusion but decrease rate and give antipyretics
 - if fever >38°C, stop transfusion, give antipyretics and anti-histamine

Allergic Nonhemolytic Transfusion Reactions

- alloantibodies (IgE) to proteins in donor plasma result in mast cell activation and release of histamine
- occurs mainly in those with history of multiple transfusions or multiparous women
- risk per unit of blood is 1 in 100
- presents mainly as urticaria and occasionally with fever
- can present as anaphylactoid reaction with bronchospasm, laryngeal edema and hypotension, but this occurs mainly in IgA deficient patients that have anti-IgA antibodies
- treatment
 - mild: slow transfusion rate and give diphenhydramine
 - moderate to severe: stop transfusion, give IV diphenhydramine, steroids, epinephrine, IV fluids and bronchodilators

Transfusion-Related Acute Lung Injury (TRALI)

- new-onset acute lung injury that occurs during transfusion or within 6 hours of the completion of transfusion
 - insidious, acute onset of pulmonary insufficiency
 - profound hypoxemia ($\text{PaO}_2/\text{FiO}_2 < 300$ mmHg)
 - bilateral pulmonary edema on CXR
 - pulmonary artery wedge pressure <18 mmHg
 - no clinical evidence of left atrial hypertension



DDx of Post-Transfusion Fever:

- Acute hemolytic transfusion reaction
- Febrile non-hemolytic transfusion reaction
- Bacterial contamination
- Allergy

DDx of Post-Transfusion Dyspnea:

- Circulatory overload
- Transfusion-related acute lung injury (TRALI)
- Allergy (bronchospasm/anaphylaxis)

- pathogenesis uncertain; perhaps due to binding of donor antibodies to WBC of recipient and release of mediators that increase capillary permeability in the lungs
- typically occurs 2-4 hrs post transfusion and resolves in 24-72 hrs
- risk per unit of blood is 1 in 5000
 - is currently the leading cause of transfusion-related morbidity and mortality
- treatment: supportive therapy (oxygen)
- inform blood bank; patient and donor testing will be arranged

NONIMMUNE

Bacterial Infection

- Gram positive: *S. aureus*, *S. epidermis*, *Bacillus cereus*
- Gram negative: *Klebsiella*, *Serratia*, *Pseudomonas*, *Yersinia*
- overall risk is 1 in 100,000 for RBC and 1 in 10,000 for platelets
- never store blood >4 hours after bag has left blood bank
- treatment: stop transfusion, blood cultures, IV antibiotics, fluids

Transfusion Associated Circulatory Overload

- due to impaired cardiac function and/or excessive rapid transfusion
- presents as dyspnea, orthopnea, hypotension, tachycardia, crackles at base of lung and increased venous pressure
- incidence is 1 in 700
- treatment: transfuse at lower rate, give diuretics and oxygen

Hyperkalemia

- due to K release from stored RBC
- risk increases with storage time and if blood is irradiated
- decreased risk if given fresh blood
- occurs in 5% of massively transfused patients
- treatment: see Nephrology, NP16

Citrate Toxicity

- occurs with massive transfusion in patients with liver disease – patients are unable to clear citrate from blood
- citrate binds to Ca and causes signs and symptoms of hypocalcemia
- treatment: IV calcium gluconate (10 ml of 10%) for every 2 units of blood

Dilutional Coagulopathy

- occurs with massive transfusion (>10 units)
- pRBC contains no clotting factors, fibrinogen, cryoprecipitate or platelets
- treatment: FFP, platelets and cryoprecipitate

Delayed Blood Transfusion Reactions

IMMUNE

Delayed Hemolytic

- due to alloantibodies to minor antigens such as Rh, Kell, Duffy, and Kidd
- level of antibody at time of transfusion is too low to cause hemolysis; later the level of antibody increases due to secondary stimulus and causes extravascular hemolysis
- occurs 5-7 days after transfusion
- presents as anemia and mild jaundice
- treatment: no specific treatment required; important to note for future transfusion

Transfusion-Associated Graft Versus Host Disease (GVHD)

- transfused T-lymphocytes recognize and react against “host” (recipient)
- occurs 4-30 days following transfusion
- most patients already have severely impaired immune systems (e.g. Hodgkin's or leukemia)
- presents as fever, diarrhea, liver function abnormalities and pancytopenia
- can be prevented by giving irradiated blood products

NONIMMUNE

Iron Overload

- due to repeated transfusions over long period of time (e.g. beta-thalassemia major)
- can cause secondary hemochromatosis
- treatment: iron chelators after transfusion

Viral Infection Risk

- HBV <1 in 82,000
- HTLV <1 in 1,000,000
- HCV <1 in 2,800,000
- HIV <1 in 4,000,000
- other infections include EBV, CMV, WNV

Common Medications

Table 28. Drugs for Anemia

Drug	Common Formulary	Mechanism of Action	Dosing Schedule	Indications	Contraindications	Side Effects
iron	Iron gluconate Iron sulphate Iron fumarate Palafer® Femiron®	Synthesis of hemoglobin	2-3 mg/kg/day of elemental iron in 3 divided doses PO	Iron deficiency anemia – treatment and prevention Pregnancy	Iron overload	In children: acute iron toxicity Constipation
B ₁₂	cyanocobalamin hydroxycobalamin Bedoz® Cobex®	Synthesis of folic acid and DNA	Up to 1000 µg/day PO	B ₁₂ deficiency	Hypersensitivity	Diarrhea
folic acid	Folic acid Novo Folacid® Folvite®	Synthesis of purines and thymidylate, thus DNA	up to 5 mg/day PO	Folic acid deficiency Pregnancy	Uncorrected pernicious anemia	Rash
erythropoietin	epoetin Epopgen® Eprex® dabrepoetin Aranesp®	Stimulation of RBC synthesis	50-1000 U/kg SC/IV, 3 times weekly	Renal failure Marrow failure Autologous blood donation	Uncontrolled hypertension Myelodysplastic syndrome	Hypertension

Aspirin Plus Dipyridamole versus Aspirin Alone After Cerebral Ischaemia of Arterial Origin (ESPRIT): Randomised Controlled Trial
Lancet 2006; 367:1665-73

Study: Randomised, controlled, open-treatment, auditing-blinded trial with mean follow-up of 3.5 years.

Patients: 2739 patients within 6 months of a transient ischemic attack or minor stroke of presumed arterial origin.

Intervention: Patients were assigned to aspirin (30-325 mg daily) with (n=1363) or without (n=1376) dipyridamole (200 mg twice daily).

Primary Outcome: The composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication, whichever happened first.

Results: Primary outcome events arose in 173 (13%) patients on aspirin and dipyridamole and in 216 (16%) on aspirin alone (hazard ratio 0.80, 95% CI 0.66-0.98; absolute risk reduction 1.0% per year, 95% CI 0.1-1.8). Addition of the ESPRIT data to the meta-analysis of previous trials resulted in an overall risk ratio for the composite of vascular death, stroke, or myocardial infarction of 0.82 (95% CI 0.74-0.91). Patients on aspirin and dipyridamole discontinued trial medication more often than those on aspirin alone (470 vs. 184), mainly because of headache.

Conclusion: The ESPRIT results, combined with the results of previous trials, provide sufficient evidence to prefer the combination regimen of aspirin plus dipyridamole over aspirin alone as antithrombotic therapy after cerebral ischaemia of arterial origin.

Antiplatelet Therapy

Aspirin (ASA)

- irreversibly acetylates COX, inhibiting TXA₂ synthesis, thus inhibiting platelet aggregation
- ASA is currently indicated for:
 - stroke and MI prophylaxis
 - to reduce the incidence of recurrent MI
 - to decrease mortality in post-MI patients
- dosage: single loading dose of 200-300 mg PO, followed by daily dose of 75-100 mg PO OD

Aggrenox®

- combination of ASA and dipyridamole
- dipyridamole increases intracellular cAMP levels, which inhibits TXA₂ synthesis, leading to decreased platelet aggregation
- hypothesized that the effects of dipyridamole potentiate antiplatelet actions of ASA
- Aggrenox® is more effective than aspirin in secondary prevention of stroke
- ongoing clinical trials will determine the best indications for this agent

Clopidogrel (Plavix®)

- ADP activates GP IIb/IIIa, allowing platelets to bind fibrinogen and aggregate
- clopidogrel and ticlopidine (Ticlid®) inhibit ADP binding to platelets, thus inhibiting aggregation
- useful for prevention of cardiovascular events in high-risk patients
- clopidogrel may cause TTP
- ticlopidine (Ticlid®) is associated with a risk of agranulocytosis and is rarely used

Glycoprotein IIb/IIIa Inhibitors

- Reopro® (abciximab), Integrelin® (eptifibatide), Aggrastat® (tirofiban)
- blocking GP IIb/IIIa receptor inhibits fibrinogen and vWF binding, leading to decreased platelet aggregation
- used most commonly in patients undergoing cardiac catheterization

Anticoagulant Therapy

- see *Approach to Treatment of Venous Thrombosis*, H32

Absolute Contraindications

- active bleeding
- severe bleeding diathesis or platelet count $<20 \times 10^9/L$ ($<20,000/mm^3$)
- intracranial bleeding, neurosurgery or ocular surgery within 10 days

Relative Contraindications

- mild-moderate bleeding diathesis or thrombocytopenia
- brain metastases
- recent major trauma
- major abdominal surgery within the past 2 days
- GI or GU bleeding within 14 days
- endocarditis
- severe hypertension (sBP >200 or dBP >120)
- recent stroke

Heparin and Warfarin

Table 29. Comparison of Heparin and Warfarin

	Heparin	Warfarin
Structure	Large anionic polymer, acidic	Small lipid soluble molecule
Route Administration	Parenteral (IV, SC)	Oral (PO)
Site of Action	Blood (via Antithrombin)	Liver
Onset	Rapid (seconds)	Slow (limited by half-life of clotting factors)
Mechanism	Accelerates activity of Antithrombin	Vitamin K antagonist, inhibits production of II, VII, IX, X, Protein C and S
Duration of Action	Acute (hours)	Chronic (days)
Acute Overdose	Protamine sulphate	IV Vitamin K + FFP
Monitoring	aPTT (intrinsic pathway)	PT/INR (extrinsic pathway)
Pregnancy	Safe (does not cross placenta)	Not used (can cross placenta), teratogenic

Adverse Reactions of Heparin

- hemorrhage: depends on dose, age, and concomitant use of antiplatelet agents or thrombolytics
- heparin-induced thrombocytopenia: associated with venous or arterial thrombosis (see Table 16)
- osteoporosis: with long term use

Low Molecular Weight Heparin (enoxaparin, dalteparin, tinzaparin)

- increased bioavailability compared to normal heparin
- increased duration of action
- SC route of administration
- do not need to monitor aPTT
- adverse reactions less common than UFH
- patients with renal failure (CrCl <30) can accumulate LMWH
- only minimally reversible with protamine sulphate

Heparin Alternatives

Danaparoid

- indicated for HIT, stable patients
- inhibits Factor Xa via antithrombin III
- SC route of administration
- monitor anti-Xa levels if renal failure or extremes in weight; cannot monitor aPTT

Hirudin

- indicated for HIT, unstable patients (ICU/CCU) requiring procedures
- direct thrombin inhibitor (natural)
- IV route of administration
- monitor aPTT levels
- risk of anti-hirudin antibodies (40-60%)
- increases INR (difficulty switching to warfarin)



Common Medications that Interact with Warfarin

Acetaminophen (interference with vit K metabolism)
NSAIDs (GI injury)
Fluconazole
Metronidazole
Sulfamethoxazole

Comparison of Fixed-Dose Weight – Adjusted Unfractionated Heparin and LMWH for Acute Treatment of Venous Thromboembolism

JAMA 2006; 296:935-42

Study: Multicentre, randomized, open-label, adjudicator-blinded, non-inferiority trial with follow up of 3 months.

Patients: 708 adult patients (mean age 60 yrs, 55% male, mean weight 83 kg) with acute venous thromboembolism (VTE).

Intervention: Patients were randomized to receive either fixed-dose, weight-adjusted subcutaneous unfractionated heparin or LMWH (dalteparin or enoxaparin). Therapy lasted for a minimum of 5 days and continued until the INR was brought within the therapeutic range with the initiation of warfarin therapy.

Primary Outcome: Recurrent VTE over 3 months of follow up and major bleeding within 10 days of randomization.

Results: There was no significant difference in the rate of recurrent VTE in the unfractionated heparin group (13 patients, 3.8%) vs. the LMWH group (12 patients, 3.4%). There was also no significant difference in the incidence of major bleeding within 10 days of randomization in the unfractionated heparin group (4 patients, 1.1%) vs. the LMWH group (5 patients, 1.4%). In 72% of patients receiving unfractionated heparin and 68% of patients receiving LMWH, treatment was administered outside of hospital.

Conclusion: Fixed-dose, weight-adjusted, subcutaneous unfractionated heparin is as effective as standard treatment with LMWH in patients with acute VTE.

Fondaparinux vs. Enoxaparin for the Prevention of Venous Thromboembolism in Major Orthopedic Surgery: A Meta-analysis of 4 Randomized Double-blind Studies

Arch Intern Med. 2002;162:1833-40

Purpose: To determine whether a subcutaneous 2.5 mg, once-daily regimen of fondaparinux sodium starting 6 hours after surgery was more effective and as safe as approved enoxaparin regimens in preventing VTE.

Study Selection: Four multicentre, randomized, double-blind trials in patients undergoing elective hip replacement, elective major knee surgery, and surgery for hip fracture (n=7344).

Results: Fondaparinux significantly reduced the incidence of VTE by day 11 (182 [6.8%] of 2682 patients) compared with enoxaparin (371 [13.7%] of 2703 patients), with a common odds reduction of 55.2% (95% CI, 45.8% to 63.1%; $p<.001$); this beneficial effect was consistent across all types of surgery and all subgroups. Although major bleeding occurred more frequently in the fondaparinux-treated group ($p=.008$), the incidence of clinically relevant bleeding (leading to death or reoperation or occurring in a critical organ) did not differ between groups.

Conclusions: In patients undergoing orthopedic surgery, 2.5 mg of fondaparinux sodium once daily, starting 6 hours postoperatively, showed a major benefit over enoxaparin, achieving an overall risk reduction of VTE greater than 50% without increasing the risk of clinically relevant bleeding.

Argatroban

- indicated for HIT, renal failure and unstable patients
- direct thrombin inhibitor (synthetic)
- IV route of administration
- monitor aPTT levels
- increases INR (difficulty switching to warfarin)

Fondaparinux

- selective inhibitor of Factor Xa
- heparin pentasaccharide analogue
- one of the newer drugs for prevention and treatment of VTE

Table 30. Recommended Therapeutic INR Ranges of Common Indications for Oral Anticoagulant Therapy

Indication	INR Range
Prophylaxis of venous thrombosis (high-risk surgery)	2.0-3.0
Treatment of venous thrombosis	
Most cases of thrombosis with antiphospholipid antibody syndrome	
Treatment of pulmonary embolism	
Prevention of systemic embolism	
Tissue heart valves	
AMI (to prevent systemic embolism)	
Valvular heart disease	
Atrial fibrillation	
Bileaflet mechanical valve in aortic position	2.5-3.5
Mechanical prosthetic mitral valves (high risk)	
Prophylaxis of recurrent myocardial infarction	

AMI = acute myocardial infarction

Table 31. Recommended Management of a Supratherapeutic INR

INR	Bleeding Present	Recommended Action
> Ther to 5.0	No	Lower warfarin dose, OR Omit a dose and resume warfarin at a lower dose when INR is in therapeutic range, OR No dose reduction needed if INR is minimally prolonged
> 5.0 to 9.0	No	Omit the next 1 to 2 doses of warfarin, monitor INR more frequently and resume treatment at a lower dose when INR is in therapeutic range, OR Omit a dose and administer 1 to 2.5 mg oral vit K in patients with increased risk of bleeding
> 9.0	No	Hold warfarin and administer 5 to 10 mg oral vit K. Monitor INR more frequently and administer more vit K as needed. Resume warfarin at a lower dose when INR is in therapeutic range
Any	Serious or life threatening	Hold warfarin and administer 10 mg vit K by slow IV infusion; supplement with prothrombin complex concentrate, fresh frozen plasma, or recombinant human factor VIIa, depending on clinical urgency. Monitor and repeat as needed.

Adapted from: Ansell, J, Hirsh, J, Hylek, E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; (6 Suppl):160s.

Chemotherapeutic Agents

Table 32. Selected Chemotherapeutic Agents

Class	Example	Mechanism of Action or Target
Alkylating Agent	<ul style="list-style-type: none"> chlorambucil, cyclophosphamide, melphalan (nitrogen mustards) carboplatin, cisplatin dacarbazine, procarbazine busulfan 	Damage DNA via alkylation of base pairs Leads to cross-linking of bases, abnormal base-pairing, DNA breakage
Antimetabolites	<ul style="list-style-type: none"> methotrexate (folic acid antagonist) 6-mercaptopurine, fludarabine (purine antagonist) 5-FU (pyrimidine antagonist) hydroxyurea 	Inhibit DNA synthesis
Antibiotics	<ul style="list-style-type: none"> adriamycin (anthracycline) bleomycin mitomycin C 	Interfere with DNA and RNA synthesis
Taxanes	<ul style="list-style-type: none"> paclitaxel docetaxel 	Stabilize microtubules against breakdown once cell division complete
Vinca-alkaloids	<ul style="list-style-type: none"> vinblastine vincristine vinorelbine 	Inhibit microtubule assembly (mitotic spindles), blocking cell division
Topoisomerase Inhibitors	<ul style="list-style-type: none"> irinotecan, topotecan (topo I) etoposide (topo II) 	Interfere with DNA unwinding necessary for normal replication and transcription
Monoclonal Antibodies	<ul style="list-style-type: none"> trastuzumab (Herceptin®) bevacizumab (Avastin®) rituximab (Rituxan®) cetuximab (Erbix®) 	HER2 VEGF CD20 EGFR
Small Molecule Inhibitors	<ul style="list-style-type: none"> imatinib mesylate (Gleevec®) erlotinib (Tarceva®) gefitinib (Iressa®) bortezomib (Velcade®) sunitinib (Sutent®) 	Bcr-Abl EGFR EGFR 26S proteasome VEGFR, PDGFR

Landmark Hematology Trials

Trial	Reference	Results
CML: Imatinib vs. IFN + Cytarabine	<i>NEJM</i> 2003; 348:994-1004	In patients with chronic-phase CML, imatinib was more effective than IFN α + cytarabine in inducing cytogenetic response and freedom from progression to accelerated phase/blast crisis
Hodgkin's Lymphoma: ABVD vs. MOPP	<i>NEJM</i> 1992; 327:1478-84	In Hodgkin's Lymphoma, ABVD regimen has equal failure-free and overall survival to MOPP + ABVD, but less myelotoxicity. ABVD is standard chemotherapy for Hodgkin's
CHOP	<i>NEJM</i> 1993; 328:1002-6	In NHL, CHOP has lowest incidence of fatal toxic reactions and shows no significant difference from 3 other regimens in response or disease-free/overall survival. CHOP is the standard for advanced NHL
CLOT	<i>NEJM</i> 2003; 349:146-53	In patients with cancer and acute venous thromboembolism, LWMH was more effective than coumadin in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding
ITP: Dexamethasone	<i>NEJM</i> 2003; 349:831-6	A four-day course of high-dose dexamethasone is effective initial therapy for adults with immune thrombocytopenic purpura
MRC	<i>NEJM</i> 2005; 353:85-6	Hydroxyurea plus low-dose aspirin is superior to anagrelide plus low-dose aspirin for patients with essential thrombocythemia at high risk for vascular events
TRICC	<i>NEJM</i> 1999; 340:409-17	A restrictive strategy of red-cell transfusion (when Hb < 70) is at least as effective as and possibly superior to a liberal transfusion strategy (when Hb < 100) in ICU patients; one possible exception is patients with an acute MI or unstable angina
Platelet transfusion threshold	<i>NEJM</i> 1997; 337:1870-5	The risk of major bleeding in patients with AML undergoing induction chemotherapy was similar whether the platelet-transfusion threshold was set at 20 or 10. Use of the lower threshold reduced platelet usage by 21.5 percent
Dose of platelet transfusion	<i>NEJM</i> 2010; 362:600-13	Low dose prophylactic platelet transfusion decreases total number of platelets transfused but increases number of transfusions without increased incidence of bleeding in patients with hypoproliferative thrombocytopenia

References

- Approach to the patient with thrombocytosis. UpToDate, Rose, BD (Ed). Waltham, MA 2009.
- Armitage JO. Treatment of Non-Hodgkin's lymphoma. *NEJM*. 1993;328:1023-1030.
- Bataille R, Harousseau J. Multiple myeloma. *NEJM*. 1997;336:1657-64.
- Bates SM and Ginsberg JS. Treatment of deep-vein thrombosis. *NEJM*. 2004;351:268-277.
- Bazemore AW, Smucker DR. Lymphadenopathy and Malignancy. *American Family Physician*. 2002;66:2103-2110.
- Bottomley SS. Causes of the hereditary and acquired sideroblastic anemias. In: UpToDate, Rose, BD (Ed). UpToDate, Waltham, MA 2006.
- Callum JL. Idiopathic Thrombocytopenia Purpura. www.hematology.utoronto.ca/assets/hematology+digital+assets/treatment+polices/idiopathic+thrombocytopenia+purpura.pdf
- Callum JL, Pinkerton PH. *Bloody Easy: Blood Transfusions, Blood Alternatives and Transfusion Reactions*. Sunnybrook and Women's College Health Sciences Centre: Toronto, 2003.
- Canadian Pediatric Society. Transfusion and risk of infection in Canada: Update 2006. *Pediatrics and Child Health*. 2005;11(3):158-162.
- Castellone DD. Evaluation of Bleeding Disorders. In *Saunders Manual of Clinical Laboratory Science*. Craig Lehman ED. WB Saunders CO, Philadelphia, PA, 1998.
- Cecil's Essentials of Medicine. Thrombocytopenia.
- Christiansen SC, et al. Thrombophilia, Clinical Factors, and Recurrent Thrombotic Events. *JAMA*. 2005; 293 (18):2353-2361.
- Cines DB and Blanchette VS. Immune Thrombocytopenic Purpura. *NEJM*. 2002;346:995-1008.
- Coates TD and Baehner RL. Causes of neutrophilia. In: UpToDate, Rose, BD (Ed), UpToDate, Waltham, MA 2006.
- Cohen K, Scadden D.T. Non-Hodgkin's lymphoma: pathogenesis, clinical presentation, and treatment. *Cancer Treat Res*. 2001;104:201-203.
- Decousus et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *NEJM*. 1998; 338: 409-415.
- Driscoll MC. Sickle Cell Disease. *Pediatrics in Review*. 28:7 259 – 286
- Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism. Seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest*. 2004; 126L 3385-4005.
- George JN. Treatment and prognosis of idiopathic thrombocytopenic purpura. In: UpToDate, Rose BD (Ed), UpToDate, Waltham, MA 2005.
- Goldman J. ABC of clinical haematology: Chronic myeloid leukaemia. *BMJ*. 1997; 314:657.
- Habermann TM, Steensma DP. Lymphadenopathy. *Mayo Clinic Proc*. 2000; 75(7):723-732.
- Hasenclever D, Diehl V, et al. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *NEJM*. 1998; 339:1506-14.
- Health Canada. Effects of Lead on Human Health. <http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/environ/lead-plomb-eng.php>
- Heaney M.L., Golde D.W. Myelodysplasia. *NEJM*. 1999; 340:1649-60.
- <http://cancernet.nci.nih.gov>
- Kovacs MJ et al. Comparison of 10-mg and 5-mg warfarin initiation monograms together with low-molecular-weight heparin for out patient treatment of acute venous thromboembolism. *Ann Intern Med*. 2003; 138: 714-719.
- Kyle RA and Rajkumar SV. Chemotherapy in multiple myeloma. In: UpToDate, Rose BD (Ed), UpToDate, Waltham, MA 2006.
- Kyle RA and Rajkumar SV. Clinical manifestations and diagnosis of Waldenström's macroglobulinemia. In: UpToDate, Rose, BD (Ed), UpToDate, Waltham, MA 2006.
- Landaw, SA. Approach to the adult patient with thrombocytopenia. In: Up To Date, Rose, BD (Ed), Up To date, Waltham, MA 2005.
- Leonardi-Bee J, Bath PM, Bousser MG, et al. Review: Dipyridamole given with or without aspirin reduces recurrent stroke. In *ACP Journal Club*. July/Aug 2005; 143 (1):10.
- Liesner RJ and Machin SJ. ABC of clinical haematology: Platelet disorders. *BMJ*. 1997;314:809.
- Liesner RJ and Goldstone AH. ABC of clinical haematology: The acute leukaemias. *BMJ*. 1997;314:733.
- Lowenberg B, Downing JR, Burnett A. Acute myeloid leukemia. 1999. *NEJM*. 341:1051-62.
- Mackie IJ, and Bull HA. Normal haemostasis and its regulation. *Blood Rev*. 1989;3:237.
- Markovic M, et al. Usefulness of soluble transferrin receptor and ferritin in iron deficiency and chronic disease. *Scan J Clin Lab Invest*. 2005; 65:571-576.
- Mead GM. ABC of clinical haematology: Malignant lymphomas and chronic lymphocytic leukaemia. *BMJ*. 1997;314:1103.
- Messinezy M and Pearson TC. ABC of clinical haematology: Polycythaemia, primary (essential) thrombocythaemia and myelofibrosis. *BMJ*. 1997; 314: 587.
- Mechanisms of severe transfusion reactions. *Transfus Clin Biol*. 2001;8:278-81.
- Pangalis GA, Vassilakopoulos TP, Boussiotis VA, Fessas P. *Semin Oncol* 1993; 20:570
- Pillot G, Chantler M, Magiera H, et al [Eds]. *The Washington Manual Hematology and Oncology Subspecialty Consult*. Lippincott Williams and Wilkins, Philadelphia PA, 2004.
- Pui C., Evans W.E. Acute lymphoblastic leukemia. *NEJM*. 1998;339:605-15.
- Rozman C., Montserrat E. Chronic lymphocytic leukemia. *NEJM*. 1995;333:1052-57.
- Sabatine MS (Ed). *Hematology-Oncology*. In *Pocket Medicine*, 2nd edition: The Massachusetts General Hospital Handbook of Internal Medicine. Lippincott Williams and Wilkins: Philadelphia PA, 2004.
- Satake N and Sakamoto K. Acute Lymphoblastic Leukemia. E-medicine 2006 accessed at: <http://www.emedicine.com/ped/topic2587.html>
- Sawyers C. Chronic myeloid leukemia. *NEJM*. 1999;340:1330-40.
- Streff MB, Smith B, Spivak JL. "The diagnosis and management of polycythemia vera in the era since the Polycythemia Vera Study Group: a survey of American Society of Hematology members' practice patterns". *Blood* 99 (4): 1144-9.
- The Merck Manual; Section 11, Chapter 133: platelet disorders.
- Thomas RH. Hypercoagulability syndromes. *Arch Intern Med*. 2001;161:2433-2439.
- U.S. Consumer Product Safety Commission. Ban of Lead-Containing Paint and Certain Consumer Products Bearing Lead-Containing Paint. <http://www.cpsc.gov/BUSINFO/regs/leadpaint.pdf>
- Valentine KA and Hull RD. Clinical use of warfarin. In: UpToDate, Rose BD (Ed), UpToDate, Waltham, MA 2006.
- Valentine KA and Hull RD. Clinical use of heparin and low molecular weight heparin. UpToDate, Rose BD (Ed), UpToDate, Waltham MA 2006.
- Wells PS, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *NEJM* 2003;349:1227-1235.
- Wilson SE, Watson HG, Crowther MA. Low-dose oral vitamin K therapy for the management of asymptomatic patients with elevated international normalized ratios: a brief review. *CMAJ*. 2004;170:821-4.

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Influenza		<i>Coccidioides immitis</i>	
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Avian Influenza (H5N1)		<i>Pneumocystis jiroveci</i> (<i>P. carinii</i>)	
H1N1 Influenza A		<i>Cryptococcus</i> spp.	
Severe Respiratory Illness (SRI)		<i>Candida albicans</i>	
Severe Acute Respiratory Syndrome (SARS)		<i>Aspergillus</i> spp.	
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Infective Endocarditis (IE)		<i>Entamoeba histolytica</i> (Amoebas)	
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Acute Diarrhea		<i>Giardia lamblia</i>	
Traveller's Diarrhea		<i>Trichomonas vaginalis</i>	
Chronic Diarrhea		<i>Trypanosoma cruzi</i>	
Peptic Ulcer Disease (<i>H. pylori</i>)		Apicomplexa	
Acute Viral Hepatitis		<i>Cryptosporidium</i> spp.	
Chronic Hepatitis B		<i>Plasmodium</i> spp. (malaria)	
Chronic Hepatitis C		<i>Toxoplasma gondii</i>	
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Skin and Soft Tissue Infections	PL2	Cestodes/Trematodes (flatworms)	
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Septic Arthritis		<i>Enterobius vermicularis</i> (pinworm)	
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Principles of Microbiology

Transmission of Infectious Diseases

Mechanisms

- direct contact
 - person-to-person (*S. aureus*, rhinovirus)
 - sexual (*N. gonorrhoeae*, *C. trachomatis*, herpes simplex virus, HIV)
 - blood-borne (HIV, hepatitis B, hepatitis C)
- respiratory droplets (*N. meningitidis*, *Bordetella pertussis*)
- aerosol (*M. tuberculosis*, varicella zoster virus, measles)
- food/water borne (*Vibrio cholerae*, *Salmonella*, hepatitis A, hepatitis E)
- zoonotic
 - animals (rabies, Q fever)
 - arthropods (malaria, Lyme disease)
- vertical
 - congenital syndromes (TORCH infections, see Obstetrics, OB19)
 - perinatal (HIV, hepatitis B, Group B *Streptococcus*)

Bacteriology

Bacteria Basics

- bacteria are prokaryotic cells that divide asexually by binary fission
- Gram stain divides most bacteria into two groups based on cell wall
 - Gram-positive: thick, rigid layer of peptidoglycan
 - Gram-negative: thin peptidoglycan layer + thicker outer membrane composed of lipoproteins and lipopolysaccharides
- preferred atmospheric growth conditions
 - aerobic: will not grow in the absence of oxygen
 - obligate anaerobes: growth only in complete absence of oxygen
 - facultative anaerobes: growth with or without oxygen

Table 1. Classification of Bacteria

	Gram-positive bacteria		Gram-negative bacteria	
	Cocci	Bacilli (rods)	Diplococci	Bacilli (rods)
Aerobes	<i>Staphylococcus</i> <i>Streptococcus</i> <i>Enterococcus</i>	<i>Bacillus</i> <i>Listeria</i> <i>Corynebacterium</i> <i>Nocardia</i>	<i>Neisseria</i> <i>Moraxella</i>	<i>Enterobacteriaceae</i> <i>Pseudomonas</i> <i>Haemophilus</i>
Anaerobes	<i>Peptostreptococcus</i>	<i>Clostridium</i> <i>Propionibacterium</i> <i>Lactobacillus</i> <i>Actinomyces</i>	<i>Veillonella</i>	<i>Bacteroides</i> <i>Fusobacterium</i>

Mechanisms of Bacterial Disease

- survival in the environment
 - spore formation and resistance to dryness (*Clostridium*, *Bacillus*), cold growth (*Listeria*), survival in water (*Legionella*)
- adherence to and colonization of skin or mucous membranes
 - fimbriae (pili): microfilaments extending through the cell wall
- invasion or crossing normal epithelial barriers
- evasion of host defense system through inhibition of:
 - phagocytic uptake: polysaccharide capsule (*S. pneumoniae*, *N. meningitidis*, *H. influenzae*) or surface proteins (*Staphylococcus*, *Streptococcus*)
 - intracellular growth (*Listeria*, *M. tuberculosis*)
- toxin production
 - exotoxins are secreted by living pathogenic bacteria and cause disease even if the bacteria is not present (*Clostridium*)
 - structural endotoxins are components of the bacterial cell wall that may be shed while living or released during cell lysis
- intracellular growth
 - *Chlamydomphila*, *Legionella*, *Listeria*, *Mycobacteria*, *Salmonella*



Gram Stain

Gram-positive = purple
Gram-negative = pink



Bacteria Not Seen on Gram Stain

Mycobacteria spp.
Treponema pallidum
Chlamydia/Chlamydophila spp.
Rickettsia



Acid-Fast Bacteria

Ziehl-Neelsen stain: heat or detergent use forces dye into cell, so it cannot be decolorized by acid-alcohol (e.g. *Mycobacteria* *Nocardia*).



- α -hemolytic indicates partial hemolysis of blood gas
- β -hemolytic indicates complete hemolysis of blood gas
- γ -hemolytic indicates no hemolysis of blood gas

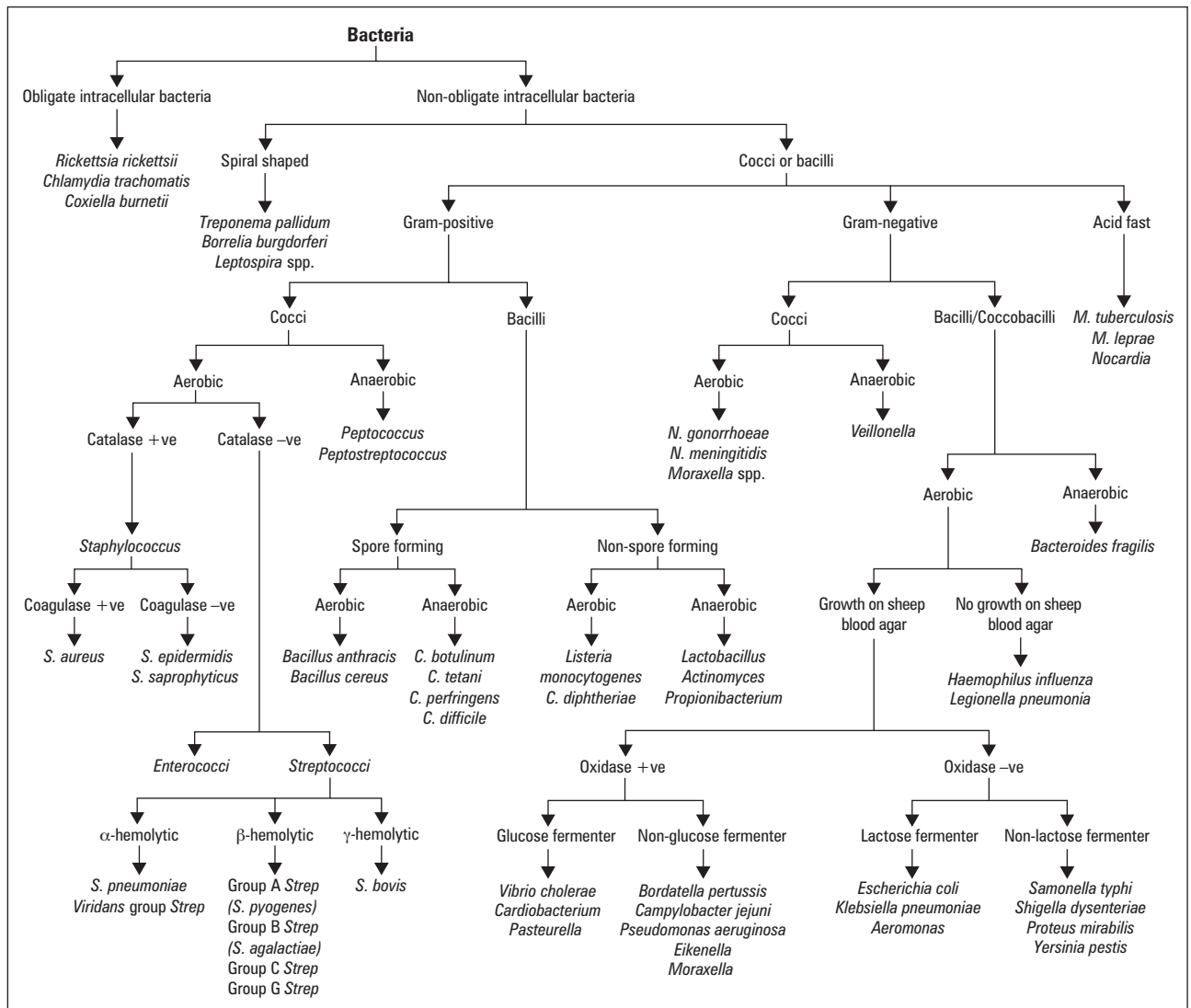


Figure 1. Laboratory Identification of Bacterial Species

Table 2. Commensal Flora

Site	Organisms
Skin	Coagulase-negative <i>Staphylococci</i> , <i>Corynebacteria</i> , <i>Propionibacterium acnes</i>
Oropharynx	<i>Viridans group Streptococci</i> , <i>Haemophilus</i> , <i>Neisseria</i> , anaerobes (<i>Peptostreptococcus</i> , <i>Bacteroides</i> , <i>Veillonella</i> , <i>Fusobacterium</i> , <i>Actinomyces</i> , <i>Prevotella</i>)
Small bowel	<i>E. coli</i> , anaerobes (low numbers)
Colon	<i>E. coli</i> , <i>Klebsiella</i> , <i>Enterobacter</i> , <i>Enterococcus</i> , anaerobes (<i>Bacteroides</i> , <i>Peptostreptococcus</i> , <i>Clostridium</i>)
Vagina	<i>Lactobacillus acidophilus</i> , <i>Viridans group Streptococci</i> , coagulase-negative <i>staphylococci</i> , facultative Gram-negative bacilli, anaerobes, <i>S. aureus</i>

Virology

Viral Basics

- viruses are nucleoprotein complexes which infect cells and use host metabolic processes to replicate
- virions are mature, released virus particles that can exist in the extracellular environment
 - composed of an internal nucleic acid core covered by a protein coat \pm glycoprotein/lipid envelope
- host susceptibility is governed by cell and virus surface proteins (viral tropism)
- host permissibility is governed by whether or not cell machinery fulfills the virus' needs
- ___**viridae** = family, ___**virus** = genus, # = species (e.g. Retroviridae HIV-2)

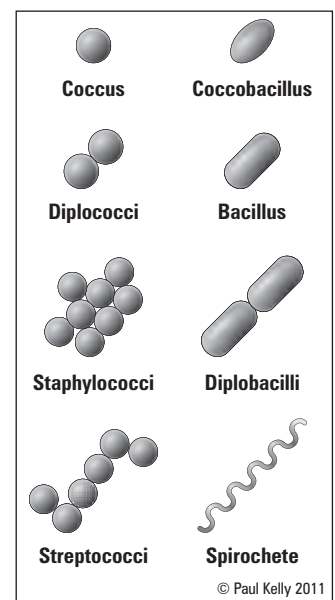


Figure 2. Bacteria Morphology

Viral Classification

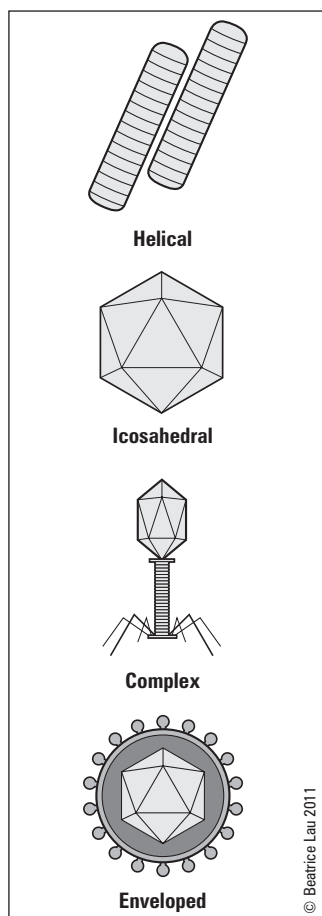
1. viral genome
 - DNA or RNA
 - ♦ RNA viruses may have a DNA intermediate made by reverse transcriptase
 - double-stranded or single-stranded
 - single or multiple pieces
2. virion shape
 - helical or icosahedral or complex
 - enveloped or naked

Viral Disease Patterns

1. acute infections
 - host cells are lysed in the process of virion release (usually naked viruses e.g. adenovirus)
 - some produce acute infections with late sequelae (e.g. measles virus → subacute sclerosing panencephalitis)
2. chronic infections (>6 months)
 - host cell machinery is used to produce and chronically release virions (usually enveloped viruses e.g. hepatitis B, HIV)
3. latent infections
 - viral genome integrated into host DNA but not actively producing virions
 - can be reactivated (e.g. herpes simplex virus)

Table 3. Common Viruses

Nucleic Acid	Enveloped	Virus Family	Major Viruses	Medical Importance
dsDNA	N	<i>Adenoviridae</i>	Adenovirus	URTI Conjunctivitis Gastroenteritis
		<i>Herpesviridae</i>	HHV1 = HSV1 HHV2 = HSV2 HHV3 = VZV HHV4 = EBV HHV5 = CMV HHV6 HHV8 = KSHV	Oral, ocular and genital herpes; encephalitis Genital, oral and ocular herpes; encephalitis Chicken pox, shingles Mononucleosis, viral hepatitis Retinitis, pneumonitis, hepatitis, encephalitis Roseola Kaposi's sarcoma, multicentric Castleman's disease, body cavity lymphoma
		<i>Papovaviridae</i>	HPV1,4 HPV6,11 HPV16,18, etc. JC virus	Plantar warts Genital warts Cervical/anal dysplasia and cancer Progressive multifocal leukoencephalopathy
		<i>Hepadnaviridae</i>	Hepatitis B	Hepatitis
		<i>Poxviridae</i>	Molluscum contagiosum Variola	Molluscum contagiosum Smallpox
		<i>Parvoviridae</i>	Parvovirus B-19	Erythema infectiosum (Fifth disease)
		<i>Caliciviridae</i>	Norwalk Hepatitis E	Gastroenteritis Acute hepatitis
		<i>Picornaviridae</i>	Poliovirus Echovirus Rhinovirus Coxsackie virus Hepatitis A	Poliomyelitis URTIs, viral meningitis URTIs Hand-foot-and-mouth, viral meningitis, myocarditis Acute hepatitis
		<i>Coronaviridae</i>	Coronavirus	URTIs, SARS
		<i>Flaviviridae</i>	Yellow Fever Dengue Fever Hepatitis C West Nile	Yellow fever Dengue fever Hepatitis Encephalitis, flaccid paralysis
(+) ssRNA-RT	Y	<i>Togaviridae</i>	Rubella	Rubella (German measles)
		<i>Retroviridae</i>	HIV	AIDS
		<i>Arenaviridae</i>	Lassa Fever	Lassa fever
		<i>Filoviridae</i>	Ebola, Marburg	Hemorrhagic fever
		<i>Orthomyxoviridae</i>	Influenza A, B, C	Influenza
		<i>Paramyxoviridae</i>	Measles Mumps Parainfluenza RSV	Measles Mumps URTIs, croup, bronchiolitis Bronchiolitis, pneumonia
		<i>Rhabdoviridae</i>	Rabies	Rabies
		<i>Reoviridae</i>	Rotavirus	Gastroenteritis
(-) ssRNA	Y			

**Figure 3. Virus Morphology**

Mycology

Fungal Basics

- fungi are strictly aerobic eukaryotic organisms with two major chemical differences from human cells
 - ergosterol is the major fungal membrane sterol (instead of cholesterol)
 - fungal cell walls contain chitin, a complex glycopolysaccharide (instead of peptidoglycans as seen in bacteria)
- two broad groups of fungi: yeast (unicellular) and molds (multicellular with hyphae)
- dimorphic fungi are generally found as mold at room temperature but grow as yeast-like forms at body temperature

Mechanisms of Fungal Disease

- primary fungal infection through
 - overgrowth of normal flora; usually yeasts or dermatophytes
 - inhalation of fungal spores
 - traumatic inoculation into skin
- toxins produced by fungi (e.g. ingestion of toxic mushrooms, aflatoxins)
- allergic reaction to fungi (e.g. bronchopulmonary aspergillosis)

Parasitology

Parasite Basics

- a parasite is an organism that lives in or on another organism (host) and damages the host in the process
- a parasite with a complex life cycle requires more than one host to reproduce
 - reservoir host maintains a parasite and may be the source for human infection
 - intermediate host maintains the asexual stage of a parasite or allows development of the parasite to proceed to the larval stage
 - definitive host allows the parasite to develop to the adult stage where reproduction occurs
- there are 2 major groups of parasites: protozoa and helminths

Table 4. Differences Between Protozoa and Helminths

Protozoa	Helminths
Unicellular	Multicellular
Motile trophozoite → inactive cyst	Adult → egg → larva
Multiplication	No multiplication
± Eosinophilia	Eosinophilia (proportional to extent of tissue invasion)*
Indefinite life span	Definite life span

*Adult ascaris (tapeworms), do not cause eosinophilia

Table 5. Common Parasites

Cellularity	Shape/Locomotion	Common Species	Medical Importance
Protozoa	Apicomplexa	<i>Cryptosporidium</i>	Diarrhea, opportunistic infection
		<i>Microsporidia</i> (<i>Enterocytozoon</i> , <i>Encephalitozoon</i>)	Diarrhea, opportunistic infection
		<i>Cyclospora</i>	Diarrhea
		<i>Plasmodium</i> spp.	Malaria
		<i>Toxoplasma gondii</i>	Systemic illness, blindness, opportunistic infection
	Amoebas	<i>Entamoeba histolytica</i> , <i>Entamoeba dispar</i>	Amoebic dysentery if <i>E. histolytica</i>
	Ciliates	<i>Balantidium coli</i>	GI disease
	Flagellates	<i>Giardia lamblia</i>	GI disease
		<i>Trichomonas vaginalis</i>	Vaginitis
		<i>Leishmania</i>	Leishmaniasis (visceral or cutaneous)
		<i>Trypanosoma cruzi</i> , <i>gambiense</i> , <i>rhodesiense</i>	Chagas, Sleeping Sickness

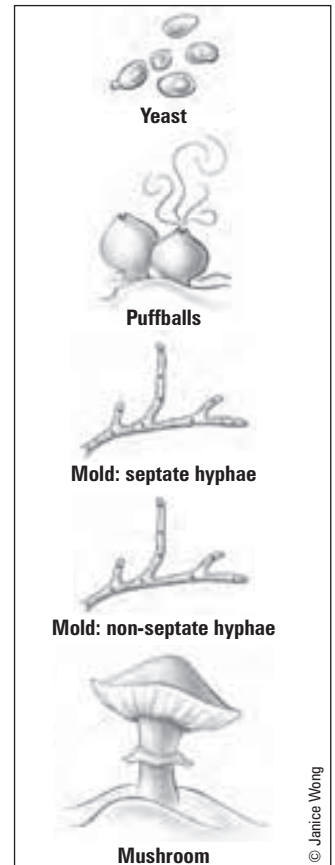


Figure 4. Common Fungus Morphology

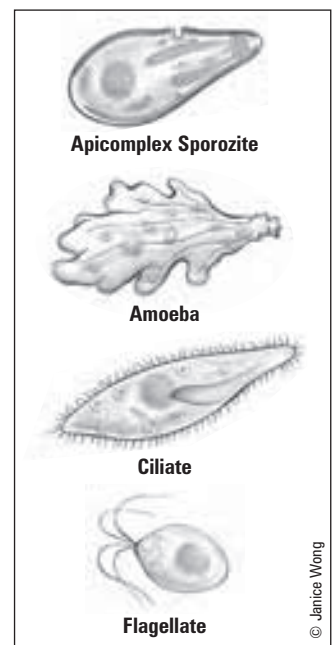


Figure 5. Basic Protozoal Morphology

Table 5. Common Parasites (continued)

Cellularity	Shape/Locomotion	Common Species	Medical Importance
Helminths	Flatworms		
	Trematodes (unsegmented): "flukes"	<i>Clonorchis sinensis</i> <i>Schistosoma mansoni</i> , <i>hematobium</i> , <i>japonicum</i>	Liver fluke, risk factor for cholangiocarcinoma Schistosomiasis, risk factor for bladder cancer
	• Use snails as intermediate hosts then infect humans via water exposure or via ingestion of 2nd intermediate host		
	Cestodes (segmented): "tapeworms"	<i>Taenia saginata</i> , <i>solium</i> <i>Diphyllobothrium lata</i>	GI disease, neurocysticercosis GI disease, vitamin B ₁₂ deficiency
	• Have multiple intermediate hosts		
	• Disease more serious in intermediate host		
	• Lives in GI tract as worm in definitive host		
	Nematodes (unsegmented): "roundworms"	Roundworms: <i>Ascaris lumbricoides</i> Pinworms: <i>Enterobius vermicularis</i> Hookworms: <i>Ancylostoma duodenale</i> Whipworms: <i>Trichuris trichiura</i>	Pulmonary and GI disease Pruritus ani GI disease, anemia GI disease
	• Humans are definitive host		
	• Lifecycles can be complex		
		Threadworm: <i>Strongyloides stercoralis</i> Filaria: <i>Wuchereria bancrofti</i> , <i>Onchocerca volvulus</i> , loa loa	GI disease, difficult to treat Elephantiasis, lymphedema, pruritis



See Tables 23 and 24, ID42, for more information on flatworms and roundworms.



Parasite sampling may need to be repeated on a number of occasions before infection can be ruled out.

Characteristics of Parasitic Disease

- spectrum of disease ranging from asymptomatic to severe illness
- symptoms are usually proportional to parasite burden
- tissue damage due to the host immune response and the parasite itself
- chronic infections may occur with or without overt disease, reinfection may occur
- immunocompromised hosts are more susceptible to manifestations of infection, reactivation of latent infections and more severe disease

Mechanisms of Parasitic Disease

1. mechanical obstruction (e.g. ascariasis, clonorchiasis)
2. competition with host for resources (e.g. anemia in hookworm disease, vitamin B₁₂ deficiency in diphyllobothriasis)
3. cytotoxicity leading to abscesses and ulcers (e.g. amoebiasis, leishmaniasis)
4. inflammatory
 - acute hypersensitivity (e.g. pneumonitis in Loeffler's syndrome)
 - delayed hypersensitivity (e.g. egg granulomas in schistosomiasis)
 - cytokine-mediated (systemic illness of malaria, disseminated strongyloidiasis)
5. immune-mediated injury
 - autoimmune (e.g. myocarditis of Chagas disease, tissue destruction of mucocutaneous leishmaniasis)
 - immune complex (e.g. nephritis of malaria, schistosomiasis)

Neurological Infections

Meningitis

- inflammation of the meninges

Etiology

Table 6. Common Organisms in Meningitis

Bacterial	Immunocompromised/ Elderly	Neonates	Viral	Fungal	Other
<i>S. pneumoniae</i>	<i>S. pneumoniae</i>	GBS	Enteroviruses	<i>Cryptococcus</i>	Lyme disease
<i>N. meningitidis</i>	<i>N. meningitidis</i>	<i>E. coli</i>	HIV	<i>Coccidioidomycosis</i>	Neurosyphilis
<i>H. influenzae</i>	<i>L. monocytogenes</i>	<i>L. monocytogenes</i>	HSV-2 West Nile		TB

Risk Factors

- hematogenous spread after invasion from a mucosal surface: respiratory tract, infectious endocarditis
- parameningeal focus (otitis media, odontogenic infection, sinusitis)
- penetrating head trauma
- anatomical meningeal defects
- previous neurosurgical procedures, shunts
- immunodeficiency (asplenia, corticosteroids, HIV, complement deficiency)
- contact with others with meningitis
- recent travel to endemic areas



Brudzinski's Sign

Passive neck flexion causes involuntary flexion of hips and knees.

Kernig's Sign

Resistance to knee extension when hip is flexed to 90°.

Jolt Accentuation of H/A

Headache worsens when head turned horizontally at 2-3 rotations/sec.



CSF Gram Stain Findings

S. pneumoniae – GP diplococci
N. meningitidis – GN diplococci
H. influenzae – Pleomorphic GN coccobacilli
L. monocytogenes – GP rods

Clinical Features

- neonates and children: fever, vomiting, lethargy, irritability, poor feeding
- older children and adults: fever, headache, neck stiffness, confusion, nausea and vomiting, lethargy, photophobia, altered level of consciousness, seizures, focal neurological signs, papilledema
- petechial rash on lower extremities with meningococcal meningitis

Investigations

- CBC with differential, blood C&S, electrolytes (for SIADH)
- x-rays may indicate primary site of spread (CXR, sinuses, mastoid bone)
- LP for CSF profile cell count and differential, chemistry (CSF glucose and protein), microbiology (Gram stain, C&S, PCR (if suspecting viral etiology), mycobacterial + fungal culture)
- CT, MRI, EEG if focality present

Table 7. CSF Profiles for Meningitis

	Bacterial	Viral
Appearance	Normal or cloudy	Normal or cloudy
Glucose (mmol/L)	Decreased	Normal
Protein (g/L)	Markedly Increased	Increased
White blood cell	500-10,000/ μ L	10-500/ μ L
Predominant WBC	Neutrophils	Lymphocytes

Treatment

- bacterial meningitis is a medical emergency: do not delay antibiotics before CT or LP
- initial empirical antibiotics
 - neonates (<1 month old): ampicillin \pm cefotaxime if >7 days old
 - infants, children, adults: vancomycin 1 g IV q12h + ceftriaxone 2 g IV q12h \pm ampicillin 2 g IV q4h if >50 years or history of alcohol use or immunocompromise
- adjust when Gram stain, C&S results become available
- dexamethasone 10 mg IV q6h x 4 days, started before or with first dose of antibiotics in suspected bacterial meningitis
 - most beneficial in turbid meningitis secondary to pneumococcal infection
- prevention
 - children: immunization against *H. influenzae* (Pentacel[®]), *S. pneumoniae* (Synflorix[®], Prevnar[®]), *N. meningitidis* (Menjugate[®], Menactra[®])
 - adult: immunization against *N. meningitidis* in selected circumstances (outbreaks, travel, epidemics) and *S. pneumoniae* (Pneumovax[®]) for high-risk groups
 - prophylaxis: rifampin or ciprofloxacin for household and close contacts of *H. influenzae* and *N. meningitidis* cases

Prognosis

- complications
 - headache, seizures, cerebral edema, hydrocephalus, SIADH, residual neurological deficit (especially CN VIII), deafness, death
- mortality
 - *S. pneumoniae* 25%; *N. meningitidis* 5-10%; *H. influenzae* 5%
 - worse prognosis with extremes of age, delays in diagnosis and treatment, stupor or coma, seizures, focal neurological signs, septic shock

Encephalitis

- inflammation of brain parenchyma

Etiology

- viral (most common)
 - HSV, mumps, measles, rabies, arboviruses (e.g. West Nile), HIV, polio, CMV
- bacteria, protozoa, and helminths are rare causes of encephalitis

Pathophysiology

- an acute inflammatory disease of the brain due to direct invasion or hypersensitivity initiated by a pathogen
- some viruses reach CNS via peripheral nerves (e.g. rabies, HSV)
- herpes simplex encephalitis
 - acute, necrotizing, asymmetrical hemorrhagic process with lymphocytic and plasma cell reaction which usually involves the medial temporal and inferior frontal lobes
 - associated with HSV-1, but can also be caused by HSV-2

Dexamethasone in Adults with Bacterial Meningitis

NEJM 2002; 347:1549-56

Study: Randomized, double blind, placebo controlled trial.

Patients: 301 patients over the age of 17 with suspected meningitis in conjunction with cloudy CSF, positive Gram stain or >1,000 leukocytes/mm³.

Intervention: Antibiotics with dexamethasone (10 mg q6h x 4 days, first dose given within 20 minutes prior to or with first dose of antibiotics) versus antibiotics with placebo.

Main Outcome: Glasgow Outcome Scale at 8 weeks (5 is favourable outcome, 4-1 is unfavourable outcome), mortality.

Results: At 8 weeks follow up, dexamethasone group was associated with fewer unfavourable outcomes than placebo (15 vs. 25%; RR=0.59, p=0.03; ARR=10%). Mortality rates were also lower in dexamethasone group than placebo (7 vs. 15%; RR=0.48, p=0.04).

Does This Adult Patient Have Acute Meningitis? From The Rational Clinical Examination

JAMA 1999; Vol 281, No. 2

Study: Systematic review of 10 studies that assessed the accuracy and precision of the clinical examination in the diagnosis of adult meningitis.

Results: Sensitivity of the clinical history is low (pooled sensitivity for headache: 50%, pooled sensitivity for nausea/vomiting: 30%, pooled sensitivity for neck pain: 28%). Two studies reported that 99-100% of patients presenting with meningitis had at least 1 of fever, neck stiffness and a change in mental status. Fever had an overall sensitivity of 85% in the diagnosis of meningitis and altered mental status had a sensitivity of 67%. The overall pooled sensitivity for neck stiffness was 70%. Kernig's and Brudzinski's signs have not been well-studied. In one study of young adults presenting with fever and headache, Kernig's sign had a sensitivity of 9% and specificity of 100% and Brudzinski's sign had a sensitivity of 15% and a specificity of 100%. Jolt accentuation of headache was assessed by one study and found to have a sensitivity of 97% and specificity of 54%. The presence of rash or focal neurological symptoms is not useful for the diagnosis of meningitis.

Conclusions: Clinical history alone is not sufficient for the diagnosis of meningitis. The absence of all three classic signs of meningitis (fever, neck stiffness, and altered mental status changes) virtually eliminates the diagnosis. Fever had the highest sensitivity among the physical signs. In patients with fever and headache, jolt accentuation of headache may be an effective maneuver in helping to distinguish which patients require a lumbar puncture. More prospective research is required to conclusively assess the accuracy of the clinical examination for meningitis.



Public Health Agency of Canada Indications for Adult Immunization

Pneumococcal polysaccharide vaccine (i.e. Pneumovax[®])

- >65 years
- >2 years, with chronic cardio/respiratory/hepatic/renal disorders, asplenia, sickle cell or immunosuppression

Meningococcal C-conjugate vaccine (i.e. Menjugate[®])

- Young adults
- Asplenia*
- Travellers to high-risk areas*
- Military recruits*
- Complement, factor D, or properdin deficiency*

*Quadrivalent vaccine (Menactra[®] or Menomune[®]) preferred

Clinical Features

- constitutional: fever, chills, malaise, nausea, vomiting
- meningeal involvement (meningoencephalitis): headache, nuchal rigidity
- parenchymal involvement: seizures, mental status changes, focal neurological signs
- herpes simplex encephalitis
 - acute onset (<1 week) of focal neurological signs: hemiparesis, ataxia, aphasia, focal or generalized seizures
 - temporal lobe involvement: behavioural disturbance
 - usually rapidly progressive over several days and may result in coma or death
 - common sequelae: memory and behaviour disturbances

Investigations

- LP for CSF profile, Gram stain, C&S, PCR (viral)
- serologic studies are valuable in diagnosing some causes of encephalitis (e.g. West Nile Virus)
- CT/MRI/EEG to define anatomical sites affected
- brain tissue biopsy for culture, histological examination, and immunocytochemistry (if diagnosis not clear via non-invasive means)
- herpes simplex encephalitis (must rule out due to high mortality)
 - CT/MRI: medial temporal lobe necrosis
 - PCR of CSF for HSV DNA: for rapid diagnosis
 - EEG: early focal slowing, periodic discharges
 - biopsy: when diagnosis uncertain

Treatment

- general supportive care plus therapy directed against specific infecting agent
- monitor vital signs carefully
- IV acyclovir empirically until herpes simplex encephalitis ruled out

Generalized Tetanus

Etiology and Pathophysiology

- *Clostridium tetani*: motile, spore forming, anaerobic Gram-positive bacillus
- found in soil, splinters, rusty nails, GI tract (humans and animals)
- traumatic implantation into tissues with low oxygenation (e.g. puncture wound, burns, nonsterile surgeries or deliveries)
- tetanus toxin acts on anterior horn cells blocking release of GABAergic inhibitory mediators leading to sustained muscle contraction (tetanic spasms)

Clinical Features

- tetanic spasms begin in jaw area causing lockjaw (trismus) and facial grimace/smile (risus sardonicus)
- paralysis descends to involve large muscle groups (neck, abdomen)
- fever, diaphoresis, hypertension and paroxysmal tachycardia may occur (autonomic hyperactivity)
- apnea and death secondary to paralysis of pharyngeal and respiratory muscles

Treatment

- management of infection
 - clean wound to debride necrotic tissue and spores
 - tetanus immune globulin (TIG) to bind exotoxin
 - IV metronidazole
- supportive therapy: intubation, spasmolytic medications (benzodiazepines), quiet environment, cooling blanket
- control autonomic dysfunction: beta-blocker, magnesium sulfate
- tetanus immunization series on discharge

Prevention

- tetanus toxoid vaccination (see [Pediatrics](#), P4/[Emergency Medicine](#), ER17)

Rabies

Etiology and Pathophysiology

- caused by infection with *Lyssavirus Rabies* (family: *Rhabdoviridae*)
- infection through bites or contamination of wounds with saliva or neural tissue
- incubation is usually several weeks to months (can range from days to years) then travels to PNS and CNS



Antimicrobial therapy (e.g. metronidazole) may fail to treat *C. tetani* unless adequate wound debridement is performed.

Clinical Features

- fever, headache, local prodrome of pain/pruritis/paresthesia/sensory loss at wound site
- acute, progressive encephalomyelitis
 - hyperactivity, agitation, confusion, seizures, hypertonia
- classic brainstem encephalitis
 - cranial nerve dysfunction, painful contraction of pharyngeal muscles when swallowing liquids resulting in hydrophobia and foaming of the mouth
 - coma and death due to respiratory centre dysfunction
 - almost always fatal once virus enters CNS and symptoms ensue
 - onset of symptoms can be prevented with post-exposure vaccine and immunoglobulin (HRIG)

Investigations

- ante-mortem: direct immunofluorescence or PCR on skin biopsy, corneal impression, saliva, viral isolation, serology
- post-mortem: direct immunofluorescence in nerve tissue, presence of Negri bodies (inclusion bodies in neurons)

Treatment and Prevention

- post-exposure prophylaxis depends on regional prevalence (contact Public Health)
- if bitten by a possibly rabid animal (e.g. unusual behaviour or wild animals):
 - sacrifice animal and examine brain for Negri bodies
 - clean wound promptly with soap and running water
 - passive immunization with Human Rabies Ig into wound site
 - active immunization with inactivated rabies virus vaccine (series of shots post-exposure)
- if animal is unlikely to be rabid:
 - capture animal and observe for 10 days
 - begin rabies post-exposure prophylaxis at first sign of rabies in animal
- vaccinate animals
- pre-exposure prophylaxis vaccination for high risk individuals
 - simplifies course of post-exposure prophylaxis by eliminating need for HRIG
 - offers partial immunity
- treatment is supportive once victim manifests signs and symptoms of encephalomyelitis

Respiratory Infections



Pneumonia

Definition

- infection of the lung parenchyma

Etiology and Pathophysiology

- infectious agent must overcome normal lung defences:
 - cough reflex, reflex closure of the glottis
 - tracheobronchial mucociliary transport
 - alveolar macrophages
 - inflammatory immune system response

Table 8. Common Organisms in Pneumonia

Community Acquired	Nosocomial	HIV-associated	Alcoholic
<i>S. pneumoniae</i>	Enteric GN rods	<i>Pneumocystis jiroveci</i>	<i>Klebsiella</i>
<i>Mycoplasma</i>	<i>Pseudomonas</i>		Enteric organisms
<i>Chlamydia</i>	<i>S. aureus</i>		GN bacilli
<i>H. influenzae</i>			<i>S. aureus</i>
Viral			Anaerobes (aspiration)

Table 9. Common Organisms in Pneumonia by Age

Age	Organism
Neonatal Viral	HSV, Enterovirus, CMV
Birth – 1 month	Group B Strep, Coliforms (<i>E. coli</i>), <i>Listeria</i> , <i>H. flu</i> (nontypeable), <i>B. pertussis</i>
1 month – 3 months	<i>S. aureus</i> , <i>H. flu</i> (nontypeable), pneumococcus, <i>Chlamydia pneumoniae</i> , <i>B. pertussis</i> , RSV, parainfluenza
3 months – 4 years	RSV, parainfluenza, human metapneumovirus, influenza, rhinovirus, pneumococcus, <i>H. flu</i> , GAS, <i>S. aureus</i> , <i>Mycoplasma</i>
Age 5+	<i>Mycoplasma</i> , <i>Chlamydia pneumoniae</i> , pneumococcus, TB
All Ages	<i>S. pneumoniae</i> , <i>S. aureus</i> , GAS, <i>Mycoplasma</i> , Adenovirus, <i>Chlamydia pneumoniae</i>



When *Klebsiella* causes pneumonia, see red currant jelly sputum

3 A's of *Klebsiella*

Aspiration pneumonia
Alcoholics and diabetics
Abscess in lungs



Fever without a concomitant rise in pulse rate may be seen in legionellosis.

Risk Factors

- increased risk when lung defences are impaired
 - poor cough/gag reflex (e.g. illness, drug-induced)
 - impaired swallowing mechanism (e.g. mechanical obstruction, dysphagia secondary to stroke/multiple sclerosis/myasthenia gravis/dementia)
 - impaired ciliary transport (e.g. smoking, cystic fibrosis)
 - immunosuppression
- increased risk of aspiration
 - altered level of consciousness, alcoholism, GERD, intubation/extubation, seizure

Clinical Features

- cough (\pm sputum), fever, pleuritic chest pain, dyspnea, tachypnea, tachycardia
- elderly often present atypically; altered LOC is sometimes the only sign
- on physical exam, may find evidence of consolidation: dullness to percussion, bronchial breath sounds, crackles, increased fremitus, and whisper pectoriloquy

Investigations

- routine labs: determine prognosis and need for hospitalization (along with history and physical examination)
- ABGs: assess adequacy of gas exchange and ventilatory insufficiency in more severe cases; oxygen saturation is sufficient in most
- CXR shows distribution (lobular consolidation or interstitial pattern), extent of infiltrate \pm cavitation
- sputum C&S and Gram stain, blood C&S, \pm pleural fluid C&S, \pm serology/viral detection
- bronchoscopy \pm washings for severely ill patients unresponsive to treatment and for the immunocompromised
- no organism found in $>50\%$ of cases

Treatment

Criteria for Hospitalization

Table 10. Fine Criteria, Prognosis and Recommended Triage

Calculate the Score by Adding the Points (PORT Score)

Variables	Features	Points
Demographic	Men	Age in years
	Women	Age -10
	Nursing home resident	+10
Coexisting problems	Neoplasm	+30
	Liver disease	+20
	CVA, renal disease, CHF	+10
Exam	Altered mental status	+20
	RR >30	+20
	SBP <90	+20
	Temp $<35^\circ$ or $>40^\circ$ ($<95^\circ\text{F}$ or $>104^\circ\text{F}$)	+15
	HR >125	+10
Laboratory	pH <7.35	+30
	BUN >10.7	+20
	Na <130	+20
	Glucose >13.9	+10
	Hematocrit $<30\%$	+10
	PaO ₂ <60 or SaO ₂ $<90\%$	+10
	Pleural effusion	+10

Class	Score	Mortality	Suggested Triage (complement with good clinical judgement)
I	Age <50 , no comorbidities	$<1.0\%$	Outpatient
II	<70	$<1.0\%$	Outpatient
III	71-90	2.8%	Brief inpatient
IV	91-130	8.2%	Inpatient
V	>130	29.2%	ICU

NEJM 1997; 336:243. Copyright 1997 Massachusetts Medical Society. All rights reserved. Adapted with permission in 2011.



CURB 65 Score – Pneumonia Clinical Prediction Tool

Confusion

Urea – >7 mmol, BUN >19

Respiratory rate – >30 breaths/min

Blood pressure – systolic <90
– diastolic <60

65 – or older in age

0-1 can treat as outpatient, 2 consider hospitalization, 3-5 consider ICU

Mortality: 0-1 $<5\%$, 2-3 $<10\%$, 4-5 $<30\%$

High-Dose, Short-Course Levofloxacin for Community-Acquired Pneumonia: A New Treatment Paradigm

Clin Infect Dis 2003; 37:752-60

Study: RCT, double blind, multi-centre trial.

Population: 530 adult patients with mild-to-severe community acquired pneumonia (CAP).

Intervention: 5-day course of 750 mg levofloxacin PO/IV daily versus 10-day course of 500 mg levofloxacin PO/IV daily.

Primary outcome: Clinical response, microbial response, and safety.

Results: Clinical success was 92.4% for 750 mg, 91.1% for 500 mg. 2 patients in the 500 mg arm had new infections within 31 days versus 3 in the 750 mg arm. 4 of the 750 mg arm had relapses of infection. 99.4% of all pathogens isolated were susceptible to levofloxacin. Number of patients with fever on day 3 of treatment was significantly lower in the 750 mg arm versus the 500 mg arm (49.1% vs. 38.5% respectively, $p=0.03$). There were no other significant differences in symptom resolution at day 3 (cough, sputum, shortness of breath, chills, pleuritic chest pain). No significant difference in microbial eradication rates between the two arms for any pathogen. Adverse effects were equal in both treatment arms.

Conclusion: A 5-day course of 750 mg levofloxacin is at least as effective as a 10-day course of 500 mg levofloxacin in the treatment of community acquired pneumonia.

Table 11. IDSA/ATS Community Acquired Pneumonia Treatment Guidelines 2007

Setting	Circumstances	Treatment	Example
Outpatient	Previously well No antibiotic use in last 3 months	macrolide OR doxycycline	clarithromycin 500 mg PO BID OR doxycycline 100 mg PO BID
	Comorbidities (listed above) Antibiotic use in last 3 months (use different class)	Respiratory fluoroquinolone (750 mg dose only) OR Beta-lactam + macrolide	levofloxacin 750 mg PO q24h OR amoxicillin 1000 mg PO TID + clarithromycin 500 mg PO BID
Inpatient	Ward	Respiratory fluoroquinolone OR Beta-lactam + macrolide	levofloxacin 750 mg PO q24h OR amoxicillin 1000 mg PO TID + clarithromycin 500 mg PO BID
	ICU	Beta-lactam PLUS azithromycin OR a respiratory fluoroquinolone	ceftriaxone 1g IV q24h + (azithromycin 500 mg IV q24h x 5 days) Step-down to oral therapy when tolerated

Beta-lactam – cefotaxime, ceftriaxone, ampicillin-sulbactam

Respiratory fluoroquinolone – moxifloxacin, gemifloxacin, levofloxacin

IDSA – Infectious Diseases Society of America

Macrolide – azithromycin, clarithromycin, erythromycin

ATS – American Thoracic Society

Table 12. IDSA/ATS Hospital/Ventilator/Healthcare-Associated Pneumonia Treatment Guidelines 2005

Setting	Treatment	Example
No multi-drug resistance (MDR) risk-factors Early onset (<5 d)	ceftriaxone OR levofloxacin, moxifloxacin, or ciprofloxacin OR ampicillin/sulbactam OR ertapenem	ceftriaxone 1 g IV q24h
Risk factors for MDR: Antibiotic use in last 3 months High frequency of antibiotic resistance in the community or in the specific hospital unit Hospitalization for 2 d or more in the last 3 months Residence in a nursing home or extended care facility Dialysis within 30 days Home wound care Family member with multidrug-resistant pathogen Immunosuppressive disease and/or therapy Late onset (>5 d)	antipseudomonal cephalosporin (cefepime or ceftazidime) OR antipseudomonal carbapenem (imipenem or meropenem) OR Beta-lactam/Beta-lactamase inhibitor (piperacillin/tazobactam) PLUS antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) OR aminoglycoside (amikacin, gentamicin, or tobramycin) PLUS for MRSA linezolid or vancomycin PLUS for Legionella ensure regime includes either a macrolide or a fluoroquinolone	piperacillin/tazobactam 4.5 g IV q8h + ciprofloxacin 400 mg IV q12h + vancomycin 1 g IV q12h for MRSA + azithromycin 500 mg IV q24h x 7 days for Legionella

Always use directed therapy against specific organism if one is found on culture (e.g. blood, sputum etc.)

Influenza

Etiology

- influenza virus A and B
- type A further divided into subtypes based on envelope glycoproteins: hemagglutinin (H) and neuraminidase (N)
- seasonal influenza
 - associated with antigenic drift (minor change changes in envelope glycoproteins)
 - main circulating influenza viruses: human-origin A (H1N1) and (H3N2) subtypes, type B
 - occur almost exclusively during winter months
- epidemic/pandemic influenza
 - associated with antigenic shift (major changes in glycoproteins – i.e. recombination of H and N from different strains/species, adaptation of animal strain to infect humans)
 - antigenic shift occurs only in type A only
- transmission: droplet, possibly airborne

Clinical Features of Seasonal Influenza

- incubation period 1-4 days
- fever, chills, cough, myalgias, arthralgias, headache
- complications: secondary bacterial pneumonia, otitis media, sinusitis

Investigations

- culture, DFA of nasopharyngeal swabs, serology

Evidence for Influenza Vaccination in Healthy Adults

Cochrane Database of Systematic Reviews
2007, Issue 2. Art. No.: CD001269
DOI:10.1002/14651858. CD001269.pub3

Study: Meta-analysis of 48 randomized and quasi-randomized studies evaluating influenza vaccines compared to placebo in humans.

Results: Inactivated vaccines were 80% efficacious against influenza when matched against the circulating strain and 50% when not matched. There was insufficient evidence to make firm conclusions regarding time missed from work, hospital admissions or complication rates. Common complications of parenteral vaccines included local tenderness and erythema. Parenteral vaccines were also associated with a significant increase in myalgias. Rare complications of influenza vaccines include Guillain-Barre syndrome (GBS) (estimated increased risk 1.6 cases per million vaccines), oculo-respiratory syndrome (only increased risk with trivalent inactivated split vaccines), Bell's Palsy (demonstrated increased risk with an intranasal virosomal vaccine). Attenuated vaccines have shown an increased risk of influenza-like illness.

Conclusions: The inactivated parenteral influenza vaccine has a documented efficacy of approximately 80% when matched to the strain of influenza. However, clinical effectiveness is much lower and has been estimated at approximately 15%. The authors of this review found insufficient evidence to recommend widespread vaccination of all adults. They recommend the continued vaccination of individuals in specific cases as an individual protection measure.

Treatment and Prevention

- primarily supportive
- zanamivir (Relenza®) and oseltamivir (Tamiflu®): decrease the duration (by about 24 hours) and severity of symptoms if given <48 hours from onset
 - may be used for prophylaxis against type A and type B
- amantadine/rimantadine for treatment and prophylaxis against type A
 - not effective against type A (H3N2), type B, or 2009 pandemic H1N1 influenza A
- vaccine for influenza A and B viruses is recommended annually for everyone
 - vaccine is reformulated each year to contain current serotypes of influenza A and B

Viral Respiratory Pandemics**AVIAN INFLUENZA (H5N1)****Epidemiology**

- infection with avian influenza (H5N1) first documented in Hong Kong in 1997
- approximately 63% mortality rate with age bracket 10-39 most affected

Transmission

- inhalation of droplet/droplet nuclei, direct and indirect contact
- bird-to-human, environment-to-human, and limited human-to-human spread

Clinical Features

- incubation period 2-8 days
- symptoms include high fever (>38°C), headache, myalgias, cough (± sputum); dyspnea develops approximately 5 days into illness
- can also have watery diarrhea, vomiting, abdominal pain, chest pain, and mucosal bleeding
- most develop pneumonia but a few have no respiratory symptoms
- often rapidly progresses to ARDS and multi-organ failure, death from respiratory failure

Investigations

- viral isolation and viral PCR of nasopharyngeal specimens

Treatment

- supportive care (ventilation, ICU)
- oseltamivir within 48 hours of onset of illness, weaker evidence for use of zanamivir

Prevention

- no vaccine currently available
- contact, droplet and airborne precautions
- chemoprophylaxis with oseltamivir if unprotected exposure

H1N1 INFLUENZA A**Epidemiology**

- novel H1N1 influenza A due to genetic reassortment of human, avian and swine strains
- outbreak of 2009 H1N1 first detected in Mexico City in March 2009
- low mortality rate with elderly population generally spared

Transmission

- similar to other influenza virus, direct contact and droplet transmission
- transmission human-to-human – NOT pig-to-human

Clinical Features

- incubation period 24-48 hours
- common clinical manifestations include cough (92%), fever (94%), sore throat (66%), nausea/vomiting (25%) and diarrhea (25%)

Case Definition

- WHO criteria requires a positive result in one or more of:
 - real-time RT-PCR
 - viral culture
 - 4-fold rise in pandemic H1N1 2009 virus-specific neutralizing antibodies

Treatment and Prevention

- neuraminidase inhibitors: oseltamivir, zanamivir, or peramivir (approved for emergency use in US, not Canada)
- 2009 pandemic H1N1 influenza A is not sensitive to amantadine or rimantadine
- prevent transmission with handwashing and isolation
- Influenza A (H1N1) 2009 Monovalent Vaccine recommended for ALL persons > 6 months of age
- post-exposure prophylaxis of oseltamivir or zanamivir for close contacts who meet one of the following criteria: adults and children <5 years at high risk for influenza complications, pregnant women and women up to 2 weeks post-partum, health care workers

SEVERE RESPIRATORY ILLNESS (SRI)

- SRI refers to severe viral pneumonias including Severe Acute Respiratory Syndrome (SARS) and influenza-like illnesses
- designated by Health Canada in order to establish surveillance for specific case definitions which will allow for implementation of infection control measures to prevent large-scale epidemics
- any person who meets the following case definitions should be reported to a local public health authority

Case Definitions

1. A person admitted to hospital with each of the following
 - fever $>38^{\circ}\text{C}$ AND cough or breathing difficulty
 - radiographic evidence consistent with SRI (infiltrates consistent with pneumonia or respiratory distress syndrome)
 - no alternate diagnosis within the first 72 hours of hospitalization
 - one or more of the following exposures/conditions:
 - ♦ recent travel to a potential zone of emergence/re-emergence of virus; close contact with a symptomatic person who has been to a potential zone of emergence/re-emergence within 10 days prior to onset of symptoms
 2. A deceased person with
 - a history of fever AND cough or difficulty breathing resulting in death
 - autopsy performed with findings consistent with SRI
 - one or more of the exposures/conditions listed in (1) or the deceased person is a laboratory worker handling live SARS-associated coronavirus
- exclusion criteria: patient has an alternate diagnosis that can fully explain their illness

SEVERE ACUTE RESPIRATORY SYNDROME (SARS)**Epidemiology**

- SARS-associated coronavirus (SARS-CoV) originated in China
- mortality rate $>10\%$

Transmission

- droplet, fomites, airborne contact in some cases
- asymptomatic infections uncommon and do not contribute to transmission

Clinical Features

- incubation period: mean of 4-5 days with maximum of 10-14 days
- initial symptoms are non-specific:
 - fever, myalgia, malaise, chills, cough, shortness of breath, tachypnea, pleurisy, diarrhea
- 2/3 of patients deteriorate and experience persistent fever, increasing shortness of breath, oxygen desaturation
- 20% require ICU admission and mechanical ventilation

Investigations

- real-time RT-PCR of sputum, nasopharyngeal aspirates, or fecal specimens in viral transport media
- antibody detection via enzyme-linked immunosorbent assay
- bronchoalveolar lavage, tissues from biopsy or autopsy

Treatment

- notify the local public health authority
- detailed questioning about respiratory illness in contacts and travel history
- negative-pressure respiratory isolation, N95 mask, gown, gloves, eye protection
- empiric therapy with broad-spectrum for community-acquired pneumonia
- ribavirin does not appear to be effective against SARS-CoV
- high-dose methylprednisolone may decrease lung damage

Cardiac Infections



Infective Endocarditis (IE)

Definition

- infection of cardiac endothelium; previously known as acute/subacute bacterial endocarditis (SBE)
- leaflet vegetation = platelet-fibrin thrombi, WBCs and bacteria

Etiology and Pathophysiology

- predisposing conditions:
 - high risk: prosthetic cardiac valve, previous IE, congenital heart disease (unrepaired, repaired within 6 months, repaired with defects), cardiac transplant with valve disease (surgically constructed systemic-to-pulmonary shunts or conduits)
 - moderate risk: other congenital cardiac defects, acquired valvular dysfunction, HCM
 - opportunity for bacteremia: intravenous drug use (IVDU), indwelling venous catheter, poor dentition, mucosal injury
- frequency of valve involvement MV >> AV > TV > PV

Table 13. Microbial Etiology of Infective Endocarditis Based on Risk Factors

Native Valve	IVDU	Prosthetic Valve (recent surgery <1 year)	Prosthetic Valve (remote surgery >1 year)
<i>Streptococcus</i> ¹	<i>S. aureus</i>	<i>S. epidermidis</i>	<i>Streptococcus</i>
<i>S. aureus</i>	<i>Streptococcus</i>	<i>S. aureus</i>	<i>S. aureus</i>
<i>Enterococcus</i>	<i>Enterococcus</i>	<i>Enterococcus</i>	<i>S. epidermidis</i>
GNB	GNB	GNB	<i>Enterococcus</i>
Other ²	<i>Candida</i>	Other	Other
	Other ³		

Organisms in bold are the most common isolates.

1. *Streptococcus* includes mainly *Viridans* group streptococci

2. Other includes less common organisms such as:

- Streptococcus bovis* (usually associated with underlying GI malignancy, cirrhosis)
- Culture-negative organisms including nutritionally-deficient streptococci, HACEK, *Bartonella*, *Coxiella*, *Chlamydia*, *Legionella*, *Brucella*
- Candida*

3. IVDU endocarditis pathogens depend on substance used to dilute the drugs (i.e. tap water = *Pseudomonas*, saliva = oral flora, toilet water = GI flora)

Clinical Features

- systemic
 - fever, chills, weakness, rigors, night sweats, weight loss, anorexia
- cardiac
 - dyspnea, chest pain, clubbing (subacute)
 - regurgitant murmur (new onset or increased intensity)
 - signs of CHF (secondary to acute MR, AR)
- embolic/vascular
 - petechiae, splinter hemorrhages, Janeway lesions (painless 5 mm pink macules on soles/palms)
 - focal neurological signs (CNS emboli), headache (mycotic aneurysm)
 - splenomegaly (subacute)
 - microscopic hematuria, flank pain (renal emboli) ± active sediment
- immune complex
 - Osler's nodes (painful, raised, red/brown, 3-15 mm on digits)
 - glomerulonephritis
 - arthritis
 - Roth's spots (retinal hemorrhage with pale centre)



Culture-negative (fastidious) Gram-negative Bacilli

HACEK

Haemophilus
Actinobacillus
Cardiobacterium
Eikenella
Kingella



Clinical Features of IE

FROM JANE

Fever
Roth's spots
Osler's nodes
Murmur
Janeway lesions
Anemia
Nail-bed hemorrhages (aka splinter hemorrhages)
Emboli

Diagnosis

- Modified Duke Criteria, see Table 14
 - definitive diagnosis if: 2 major, or 1 major + 3 minor, or 5 minor
 - possible diagnosis if: 1 major + 1 minor, or 3 minor

Table 14. Modified Duke Criteria

Major Criteria

Positive blood cultures for IE

Typical microorganisms for IE from 2 separate blood cultures (*Streptococcus viridans*, HACEK group, *Streptococcus bovis*, *Staphylococcus aureus*, community-acquired enterococci) OR

Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood drawn >12hrs apart or all of 3 or a majority of 4 or more separate blood cultures, with first and last drawn >1hr apart

Single positive blood culture or *Coxiella burnetii* or antiphase I IgG antibody titer >1:800

Evidence of endocardial involvement

Positive echocardiogram for IE (oscillating intracardiac mass on valve or supporting structures, or in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation OR abscess OR new partial dehiscence of prosthetic valve)

New valvular regurgitation (insufficient if increase or change in preexisting murmur)

Minor Criteria

Predisposing condition (abnormal heart valve, IVDU)

Fever (38.0°C/100.4°F)

Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, ICH, conjunctival hemorrhages, Janeway lesions

Immunologic phenomena: glomerulonephritis, rheumatoid factor, Osler's nodes, Roth's spots

Positive blood culture but not meeting major criteria OR serologic evidence of active infection with organism consistent with IE

Echocardiographic minor criteria eliminated

Investigations

- blood work: anemia (normochromic, normocytic), increased ESR, +RF
- urinalysis: proteinuria
- serial blood cultures: 3 sets (each containing one aerobic and one anaerobic sample) collected from different sites >1 h apart (definitive diagnosis)
 - may collect further samples q24-48h during treatment until patient defervesces to document response
 - samples post-treatment to document clearance of infection
- Echo: vegetations, regurgitation, abscess
 - serial echo may help in assessing cardiac function
- TEE indicated if TTE is non-diagnostic or if abscess/perforation/infection suspected
 - TTE inadequate in 20% (obesity, COPD, chest wall deformities)
- ECG: increased PR interval may indicate perivalvular abscess

Treatment

- medical
 - empiric antibiotic therapy (minimum 4 weeks)
 - first-line: cloxacillin 2 g IV q4h + gentamicin 1 g/mg IV q8h
 - if native valve and non-IVDU: add ampicillin 2 g IV q4h
 - if prosthetic valve: add rifampin 600 mg PO OD
 - prophylaxis only for high risk individuals listed above
 - targeted antibiotic therapy dependent on clinical scenario and suspected infecting organism
- dental/respiratory/esophageal procedures: amoxicillin 2 g PO/IM/IV 30-60 min prior; clindamycin 600 mg PO/IM/IV if penicillin-allergic
- GU/GI (excluding esophageal) procedures: no longer recommended
- surgical
 - relative indications: refractory CHF, valve ring abscess, fungal etiology, valve perforation, unstable prosthesis, ≥ 2 major emboli, antimicrobial failure (persistently positive blood cultures), mycotic aneurysm, staphylococci on a prosthetic valve

Prognosis

- adverse prognostic factors: CHF, prosthetic valve infection, valvular/myocardial abscess
- mortality up to 30%

Gastrointestinal Infections

Acute Diarrhea

- see [Gastroenterology](#), G14

Definition

- passage of >3 loose or liquid stools/day or >200 g stool/day for >2 days but <14 days
- termed pseudodiarrhea if above criteria not met

Table 15. Pathogens in Infectious Diarrhea

Pathogen	Source	Incubation	Symptoms	Duration	Treatment	Notes
Bacteria (invasive)						Dx: stool WBC+, RBC+, C&S
<i>Campylobacter jejuni</i>	Uncooked meat, especially poultry	2-10 days	Prodrome of fever, headache, myalgia, and/or malaise precedes diarrhea, abdominal pain and fever	<1 week	Supportive (macrolide or fluoroquinolone if >1 week or bloody diarrhea)	Most common bacterial cause of diarrhea in Canada
Enteroinvasive <i>E. coli</i> (EIEC)	Contaminated food/water	1-3 days	Fever, abdominal pain, tenesmus, scant stool containing mucus and blood	7-10 days	Supportive only, treatment hastens the resolution of symptoms, particularly in severe cases	Relatively uncommon
<i>Salmonella typhi</i> <i>S. paratyphi</i> (aka Enteric Fever, Typhoid)	Fecal-oral Contaminated food/water	10-14 days	Sudden onset crampy abdo pain and diarrhea, prolonged fever (up to 4wks if untreated), headache, rash ("rose spots")	<5-7 days diarrhea	Empiric treatment with ceftriaxone or azithromycin Fluoroquinolone 1st-line if susceptible	Extremes of age, gallstones predispose to chronic carriage increasing quinolone resistance
Non-typhoidal Salmonellosis <i>S. typhimurium</i> , <i>S. enteritidis</i>	Contaminated animal food products, especially eggs, poultry, meat, milk	12-72 hrs	Nausea, vomiting, diarrhea, abdo cramping, fever >38°C	3-7 days diarrhea, <72 hrs fever	Supportive Ciprofloxacin – not recommended except in extremes of age, immunosuppression, aneurysms, prosthetic valve grafts/joints	
<i>Shigella dysenteriae</i>	Fecal-oral Contaminated food/water	1-4 days	Fever, malaise, anorexia, limited watery diarrhea, progressing to frequent passage of small, bloody, mucopurulent stools	<1 week	Ciprofloxacin Antidiarrheals may increase risk of toxic megacolon	Very small inoculum needed for infection Complications include toxic megacolon, HUS
<i>Yersinia enterocolitica</i> <i>Y. pseudotuberculosis</i>	Contaminated food Unpasteurized milk	5 days	Acute diarrhea, low-grade fever, cramping, nausea, vomiting, hematochezia	2 weeks to months	Supportive Fluoroquinolones only for septicemia, metastatic focal infections, or immunosuppression and enterocolitis	Majority cases in children 1-4 yrs Mesenteric adenitis and terminal ileitis forms without diarrhea mimicking appendicitis
Bacteria (non-invasive/toxin-mediated)						Dx: clinical
<i>B. cereus</i> – Type A (emetic) (preformed exotoxin)	Rice dishes	1-6 hrs	Nausea, vomiting, cramps	<12 hrs	Symptomatic	
<i>B. cereus</i> – Type B (diarrheal) (secondary endotoxin)	Meats, vegetables, dried beans, cereals	8-16 hrs	Large volume watery diarrhea	<24 hrs	Symptomatic	
Enterotoxigenic <i>E. coli</i> (EHEC/STEC) i.e.: O157:H7	Verotoxin (aka Shiga-like toxin) Fecal-oral, contamination of hamburger, raw milk, drinking and recreational water	3-8 days	Grossly bloody diarrhea, fever often absent	5-10 days	Supportive Monitor renal function Antibiotics and antidiarrheals may increase risk of HUS	10% develop hemolytic uremic syndrome (HUS), which has 3-5% mortality (especially in children and elderly)
Enterotoxigenic <i>E. coli</i> (ETEC) (colonization of colon + enterotoxin production)	LT and/or ST toxins Contaminated food/water	1-3 days	Watery diarrhea, cramps	3 days	Supportive Loperamide (Imodium®) Quinolone or azithromycin	Most common cause of traveller's diarrhea

Table 15. Pathogens in Infectious Diarrhea (continued)

Pathogen	Source	Incubation	Symptoms	Duration	Treatment	Miscellaneous
Bacteria (non-invasive/toxin-mediated)						
<i>Clostridium difficile</i>	Normally present in colon in small numbers	Unclear	Unformed to watery or mucoid stools with characteristic odour	Unclear	1st line – metronidazole (PO/IV) 2nd line – vancomycin PO	Usually follows antibiotic treatment (especially clindamycin), can develop pseudomembranous colitis
<i>Clostridium perfringens</i> (secondary enterotoxin)	Contaminated food, especially meat and poultry	8-12 hrs	Sudden onset watery diarrhea, cramps, rarely vomiting	<24 hrs	Supportive Antibiotics not effective as disease is toxin mediated	<i>Clostridium</i> spores are heat resistant
<i>Staphylococcus aureus</i> (heat-stable preformed exotoxin)	Unrefrigerated meat and dairy products (custard, pudding, potato salad, mayo)	2-4 hrs	Sudden onset severe nausea, cramps, vomiting, prostration, diarrhea	1-2 days	Supportive ± antiemetics	
<i>Vibrio cholerae</i>	Contaminated food/water, especially shellfish	1-3 days	Painless voluminous diarrhea without abdominal cramps or fever	3-7 days	Aggressive fluid and electrolyte resuscitation Tetracycline or quinolones (ciprofloxacin)	Massive watery diarrhea (1-3 L/d) Mortality <1% with treatment
Parasites						Dx: stool ova and parasites (O&P)
<i>Cryptosporidium</i>	Fecal-oral	7 days	Non-bloody, watery diarrhea, fever	1-20 days	Nitazoxanide paramomycin	
<i>Entamoeba histolytica</i>	Worldwide endemic areas Fecal-oral	2-4 weeks	Ranges from asymptomatic to severe grossly bloody diarrhea Fever, weight loss	variable	Metronidazole + iodoquinol if invasive Only iodoquinol for non-invasive	May resemble IBD. If untreated, potential for liver abscess Sigmoidoscopy shows flat ulcers with yellow exudates
<i>Entamoeba dispar</i>					Supportive	Non-pathogenic Indistinguishable from <i>E. histolytica</i> microscopically (morphological)
<i>Giardia lamblia</i>	Fecal-oral (daycare #1) Contaminated food/water (travel related “beaver fever”)	1-4 weeks	Ranges from asymptomatic to acute watery diarrhea with abdominal pain to protracted course of flatulence, abdominal distention, and anorexia	Variable	Metronidazole Treatment of asymptomatic carriers not generally recommended	May need duodenal biopsy Higher risk in men who have sex with men (MSM) and immunodeficiency (IgA decreased), and daycares/nurseries
Viruses						
Rotavirus	Fecal-oral	2-4 days	Watery diarrhea, vomiting, fever	3-8 days	Supportive Vaccine available, given at 2, 4 and 6 months of age	Can cause severe dehydration Virtually all children are infected by 3 years of age
Norovirus (includes Norwalk virus)	Fecal-oral	24 hrs	Nausea, vomiting, abdominal cramps, loose watery diarrhea	24 hrs	Supportive	Often causes epidemics

Approach to the Patient with Acute Diarrhea

- symptomatic treatment, fluid and electrolyte replacement for all
- thorough history including symptoms, duration of illness, antibiotic use, travel, and sick contacts
- if >1 day of symptoms get a stool sample and examine for WBC:
 - stool smeared on slide and methylene blue drops added; >3 PMNs in 4 high power fields (HPFs) = positive
 - – WBC = non-inflammatory: continue symptomatic therapy
 - + WBC = inflammatory (infectious, IBD, radiation colitis):
 - ♦ culture for *Salmonella*, *Shigella*, *C. jejuni*, *E. coli*
 - ♦ test for *C. difficile* cytotoxin A and B if recent/remote antibiotic use or recent chemotherapy
 - ♦ consider empiric therapy with a quinolone based on severity of illness
 - ♦ flexible sigmoidoscopy: biopsies useful to distinguish inflammatory bowel disease (Crohn's disease and ulcerative colitis) from infectious colitis or acute self-limited colitis
- if >10 days consider parasitic infection *Giardia*, *Entamoeba histolytica* and send stool for ova and parasites
 - may need 3 stool samples because of sporadic passage
 - also consider post-infectious IBS
- antibiotics prolong excretion of non-typhoidal Salmonellosis and may cause *C. difficile* infection
 - clearly indicated: *Salmonella typhi*, *Shigella*, *V. cholerae*, *C. difficile*, *Cryptosporidium*, *Entamoeba histolytica*, immunocompromised patients
 - indicated in some situations: non-typhoid *Salmonella*, *Campylobacter*, *Yersinia*, *Giardia*, *ETEC* (determined by severity of illness)

Traveller's Diarrhea

Epidemiology

- up to 50% of travellers to developing countries affected in first 2 weeks and 10-20% after returning home

Etiology

- bacterial (80-90%): *E. coli* most common (ETEC), *Campylobacter*, *Shigella*, *Salmonella*, *Vibrio* (non-cholera); wide regional variation (e.g. *Campylobacter* more common in Southeast Asia)
- viral: norovirus, rotavirus, and astrovirus account for 5-8%
- protozoal (rarely): *Giardia*, *Entamoeba histolytica*, *Cryptosporidium*, *Cyclospora* for ~10% in long-term travelers
- pathogen-negative TD common despite exhaustive microbiological work-up

Prophylaxis

- bismuth subsalicylate (Pepto-Bismol®), 2 tablets (525 mg) QID up to 3 weeks (60% effective)
- antibiotic prophylaxis not routinely recommended except in high-risk travellers
 - e.g. diabetes mellitus, renal failure, inflammatory bowel disease (90% effective)
- proper hygiene practice, especially when eating at restaurants

Treatment

- usually self-limited; 90% last less than 1 week
- symptomatic, rehydration
- single-dose ciprofloxacin in moderate-severe illness (most TD bacterial)
- antimotility agents (e.g. loperamide) as adjunct to antibiotic therapy and symptomatic relief
- rehydrate with sealed or carbonated beverages; in severe fluid loss use oral rehydration solutions (1 pkg in 1L boiled or treated water)
- if lasts >10 days consider parasitic infection (*Cryptosporidium*, *Giardia*, *Entamoeba histolytica*, *Cyclospora*) and send stool for ova and parasites; also consider post-infectious IBS

Chronic Diarrhea

- see [Gastroenterology](#), G16

Peptic Ulcer Disease (*H. pylori*)

- see [Gastroenterology](#), G12

Acute Viral Hepatitis

- see [Gastroenterology](#), G32

Definition

- viral hepatitis lasting <6 months

Clinical Features

- most are subclinical
- prodrome may precede jaundice by 1-2 weeks
 - nausea, vomiting, anorexia, taste/smell disturbance
 - headaches, fatigue, malaise, myalgias
 - low-grade fever may be present
 - arthralgia and urticaria (especially hepatitis B)
- 50% progress to icteric (clinical jaundice) phase, lasting days to weeks
 - pale stools and dark urine 1-5 days prior to icteric phase
 - hepatomegaly plus RUQ pain
 - splenomegaly and cervical lymphadenopathy (10-20% of cases)

Investigations

- hepatocellular necrosis causes increased AST, ALT >10-20x normal
- ALP and bilirubin minimally elevated
- viral serology, IgM



Risk of Contracting Blood-borne Viruses from Needle Puncture

HBV	30%
HCV	3%
HIV	0.3%

Treatment

- see Gastroenterology, G35
- supportive (hydration, diet)
- indications for hospitalization: encephalopathy, coagulopathy, severe vomiting, hypoglycemia

Prognosis

- see Gastroenterology, G35
- poor prognostic indicators
 - comorbidities
 - persistently high bilirubin (>340 mmol/L; 20 mg/dL), increased INR, decreased albumin, hypoglycemia
- cholestasis – most commonly during hepatitis A virus (HAV) infection

Table 16. Characteristics of the Viral Hepatitides

	HAV	HBV	HCV	HDV	HEV	CMV	EBV	Yellow Fever
Virus Family	<i>Picornaviridae</i>	<i>Hepadnaviridae</i>	<i>Flaviviridae</i>	<i>Deltaviridae</i>	<i>Caliciviridae</i>	<i>Herpesviridae</i>	<i>Herpesviridae</i>	<i>Flavivirus</i>
Genome	RNA	DNA	RNA	RNA	RNA	DNA	DNA	RNA
Envelope	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Transmission	Fecal-oral	Parenteral, sexual	Parenteral, sexual	Parenteral, sexual	Fecal-oral	Close contacts Most body fluids	Saliva-oral	Vector
Incubation	2-6 weeks	6 weeks-6 months	2-26 weeks	3-13 weeks	2-8 weeks	20-60 days	30-50 days	3-6 days
Onset	Usually abrupt	Usually insidious	Insidious	Usually abrupt	Usually abrupt	Variable	Variable	Usually abrupt
Chronicity	None	5% adults, 90% infants	80%	5%	None	Reactivation	Reactivation	None
Oncogenicity	No	Yes	Yes	?	No	No	Yes	No
Mortality (acute)	0.1-0.3%	0.5-2%	1%	2-20% coinfection with HBV, 30% superinfection	1-2% overall, 10-20% in pregnancy			20-60% in developing countries
Immunity	Yes	Yes	?	Yes	?	?	?	Yes
Vaccine	Havrix® 2 doses q6mo combined Twinrix® at 0, 7, 21d	Recombivax HB™ age 11-15: 2 doses q6mo adults: 3 doses at 0, 7, 21d	No	No	No	No	No	YF-VAX® 1 dose booster q10yrs

Chronic Hepatitis B

Epidemiology

- develops in ≤5% of healthy adults with acute HBV hepatitis and 90% of those infected at birth
- accounts for approximately 10% of chronic hepatitis in North America
- high risk groups: IVDU, chronic hemodialysis patients, men who have sex with men

Clinical Features

- many asymptomatic
- if symptomatic, generally only mild and intermittent fatigue; correlates poorly with disease severity
- signs and symptoms of liver disease: advanced histological disease



Generally liver damage is caused more by the immune response to hepatitis B virus than from the virus itself.

Types of Chronic Infection

- perinatal infection: active viral replication, normal ALT/AST, HBeAg positive, high HBV DNA
- active infection: viral replication, elevated ALT/AST, HBeAg positive, HBV DNA >100 000 copies/ml, high infectivity, increased liver injury
- inactive (formerly termed chronic persistent hepatitis or carrier): ALT/AST normal, HBeAg negative, anti-HBe positive, HBV DNA <100 000 copies/ml, low infectivity and minimal liver injury
 - virus reactivation can occur at any time, especially if immunosuppressed (e.g. corticosteroids, lymphoma)
 - reactivation clinically resembles acute hepatitis B
- “core or precore mutant”: active virus replication with elevated HBV DNA but HBeAg negative because of promoter gene mutation
 - poor prognosis, difficult to treat

Treatment

- see [Gastroenterology](#), G33
- no treatment is indicated if in immune-tolerant, inactive carrier/low replicative, or latent HBV infection phases
- treatment of chronic replicative hepatitis with alpha-interferon, pegylated or regular
 - 24 week course of 180 µg SC 1x per week or 5 million units SC OD or 10 million units SC 3x/week
 - increases annual rate of cessation of viral replication from 7% to 40%; loss of HBsAg less common
 - relapse after successful therapy is rare (1 to 2%)
- lamivudine (Heptovir®): resolves hepatic inflammation and leads to HBeAg negative/anti-HBe positive ("seroconversion") in >90% of patients
 - 100 mg PO OD
 - relapse common when drug is stopped; drug resistance can develop after 1-2 years of use
- other antivirals used in hepatitis B treatment include adefovir dipivoxil, entecavir and tenofovir (nucleoside analogues used to decrease viral load)
- end-stage treatment is transplant, although reinfection occurs in 80-100%
- recurrence reduced with use of HBIG
- increased incidence of hepatocellular carcinoma (HCC), especially if HBeAg positive, cirrhosis, male



Suspect HDV superinfection if sudden worsening of chronic hepatitis B.

Hepatitis D Virus (HDV)

- requires HBsAg for replication, therefore infection only occurs in the presence of hepatitis B
 - co-infection: HBV and HDV acquired at the same time
 - superinfection: HBV acquired first, then HDV
- HDV increases severity of hepatitis but does not increase risk of progression to chronic hepatitis
- treatment
 - low-dose interferon has limited impact, high-dose under investigation
 - liver transplant for end-stage disease more effective than in HBV alone; reinfection rate 100% but infection usually mild

Table 17. Hepatitis B Serology

	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc	ALT, AST
Acute HBV	+	–	+	–	IgM	Elevated
Chronic Active HBV (high infectivity)	+	–	+	–	IgG	Elevated
Chronic Inactive HBV (low infectivity)	+	–	–	+	IgG	Normal
Recovery	–	+	–	+	IgG	Normal
Immunization	–	+	–	–	–	Normal

Chronic Hepatitis C

Epidemiology

- most common chronic liver disease; antibody prevalence in the USA is 1.6%
- 60-80% of acute HCV infections go on to become chronic; of those 20-30% go on to cirrhosis, and of those 25% per year develop HCC
- key findings include abnormal AST, history of IVUDU, and history of blood transfusion <1992
- time course:
 - clinical chronic hepatitis at 10 years
 - cirrhosis at 20-30 years
 - HCC at 30 years
 - time course accelerated if co-infected with HIV

Clinical Features

- usually asymptomatic
- may have non-specific symptoms: fatigue, nausea, anorexia, myalgia, arthralgia, weakness, weight loss, abdominal pain, pruritis, dark urine, cognitive impairment

Investigations

- anti-HCV: positive in chronic and resolved acute infections
- HCV RNA: positive in chronic, negative in resolved acute infection

Treatment

- see Gastroenterology, G33
- ondansetron 4 mg PO BID for fatigue
- pegylated interferon + ribavirin for 48 weeks; dosing dependent on patient weight and HCV genotype
 - 30-50% are non-responders
 - HCV RNA decrease of 2 log at 4-8 weeks is strongly predictive of response to therapy
 - multiple side effects including depression and fever/chills/malaise from interferon use, hemolytic anemias commonly from ribavirin
- HAV and HBV vaccination suggested if HCV patient is not immune



Must exclude autoimmune hepatitis because in this case interferon will worsen disease.

Renal Infections

Acute Pyelonephritis

Definition

- infection of the renal parenchyma with local and systemic manifestations
- classified as uncomplicated or complicated (i.e. immunocompromised states, presence of anatomic or functional impairment of urine flow)
- examples of complicated pyelonephritis include infection in the setting of renal or ureteric stones, strictures, prostatic obstruction (hypertrophy or malignancy), vesicoureteric reflux, neurogenic bladder, catheters, DM, sickle-cell disease, polycystic kidney disease, immunosuppression, post-renal transplant and during pregnancy

Etiology

- usually ascending microorganisms, most often bacteria
- causative microorganisms: *E. coli*, *Klebsiella*, *Proteus*, *Enterococcus*, *S. saprophyticus*
- in uncomplicated pyelonephritis, *E. coli* is most common pathogen
- suspect other less common organisms if history of instrumentation
- suspect resistant GN or even fungi in hospital patients with indwelling catheters
- GP cocci (e.g. *S. aureus*) in urine may represent bacteremia

Clinical Features

- rapid onset (hours to a day)
- fever, chills, nausea, vomiting, myalgia, malaise
- costovertebral angle (CVA) tenderness or exquisite flank pain
- lower urinary tract irritative symptoms (urgency, frequency, dysuria)
- may have symptoms of GN sepsis
- atypical presentation in the elderly: confusion may be the only symptom

Investigations

- urine
 - dipstick: +ve for leukocytes and nitrites, possible hematuria
 - microscopy: >5 WBC/HPF in unspun urine or >10 WBC/HPF in spun urine, bacteria, \pm WBC casts
 - Gram stain: GN bacilli, GP cocci
 - C&S: >10⁵ colony forming units (CFU)/mL in clean catch MSU or >10² CFU/mL in suprapubic aspirate or catheterized specimen
- blood
 - CBC + differential: leukocytosis, high % neutrophils, left-shift
 - blood cultures: may be positive in 20% of cases
- consider investigation of complicated pyelonephritis if:
 - fever, pain, leukocytosis not resolving with treatment within 72 hours
 - male patient
 - abnormal urinary tract anatomy
 - abdo/pelvic U/S, CT for renal abscess, CT for stones, cystoscopy

Treatment

- 14-day course of TMP/SMX or alternative agent to which isolate is susceptible; 7-day course of ciprofloxacin if uncomplicated
- can treat as outpatient with PO meds if mild-moderate illness, hemodynamically stable, young, otherwise healthy, uncomplicated, tolerating PO meds and fluids, adequate follow-up arranged
- otherwise start with IV for several days and then switch to PO
- if kidney completely obscured by gas (emphysematous pyelonephritis) → emergency nephrectomy
- patient more than mildly symptomatic or complicated pyelonephritis in the setting of stone obstruction is a urologic emergency (increasing risk of kidney loss or septic shock)

Prognosis

- recurrent infections often constitute relapse rather than re-infection



Common Micro-organisms Responsible for UTI/Pyelonephritis

KEEPS

Klebsiella
E. coli
Enterococcus
Proteus
S. saprophyticus



Diabetics are predisposed to emphysematous pyelonephritis.

Bone and Joint Infections

Septic Arthritis

Routes of infection

- hematogenous (adults)
- contiguous osteomyelitis (children)
- direct inoculation via skin/trauma
- iatrogenic (surgery, arthroscopy, arthrocentesis)

Etiology

- gonococcal
 - *N. gonorrhoeae*: previously accounted for 75% of septic arthritis in young sexually active adults
- non-gonococcal
 - *S. aureus*: affects all ages, rapidly destructive, accounts for most non-gonococcal cases of septic arthritis in adults (especially in those with rheumatoid arthritis)
 - *Streptococcus* species (*pyogenes*, Group A and B)
 - Gram-negatives: affects neonates, elderly, IVDU, immunocompromised
 - *S. pneumoniae*: affects children
 - *Kingella kingae*: affects children aged <2 years since HIB immunization
 - *Salmonella* spp.: characteristic of sickle cell disease
 - coagulase-negative *Staphylococcus* species (CNST): prosthetic joints
- if culture negative: *Borrelia* spp. (Lyme disease) or *Tropheryma whippelii* (Whipple's disease)

Risk Factors

- gonococcal
 - age (<40 years old), recent menses, pregnancy, MSM
- non-gonococcal
 - bacteremia (extra-articular infection with hematogenous seeding, endocarditis)
 - damaged/prosthetic joints
 - compromised immunity (diabetes, chronic kidney disease, alcoholism, cirrhosis)
 - loss of skin integrity (cutaneous ulcer, psoriasis)

Clinical Features of Gonococcal Arthritis

- two forms (although overlap often):
 - bacteremic form:
 - ♦ systemic symptoms: fever, malaise, chills
 - ♦ gonococcal triad: migratory polyarthralgias, tenosynovitis, dermatitis (pustular skin lesions)
 - septic arthritis form:
 - ♦ local symptoms in involved joint: swelling, warmth, pain, inability to bear weight, marked decrease in range of motion (see Rheumatology, RH3 for differential diagnosis)

Clinical Features of Non-gonococcal Arthritis

- acute onset of pain, swelling, warmth ± fever, chills
- most often in large weight bearing joints (knee, hip, ankle) and wrists
- usually monoarticular (polyarticular risk factors: rheumatoid arthritis, endocarditis, Group B *Streptococcus*)

Investigations

- culture and sensitivity
 - gonococcal: blood and urine C&S, as well as endocervical, urethral, rectal and oropharyngeal cultures
 - non-gonococcal: blood and urine C&S
- arthrocentesis (synovial fluid analysis) is mandatory: CBC and diff, Gram stain, culture, examine for crystals
 - infectious = opaque, increased WBC count (inflammatory), PMNs >85%, culture positive
 - growth of GC from synovial fluid is successful in <50% of cases
- ± plain x-ray: assess for osteomyelitis, provides baseline to monitor treatment



Medical Emergency

Septic arthritis is a medical emergency! If untreated, rapid joint destruction will occur.



Gonococcal Triad

- Migratory arthralgias
- Tenosynovitis next to inflamed joint
- Pustular skin lesions

Treatment

- medical
 - start IV antibiotics empirically, delay may result in joint destruction
 - use cloxacillin or cefazolin + ciprofloxacin or gentamicin if risk for Gram-negative (e.g. cloxacillin + ciprofloxacin in elderly) before culture results come back
 - consider vancomycin instead of cloxacillin or cefazolin if the patient at risk for MRSA
 - Gram stain guides subsequent treatment
 - gonococcal: ceftriaxone 1 g q24h IM or IV, doxycycline in non-pregnant patients for concurrent treatment of *C. trachomatis*
 - non-gonococcal: antibiotics against *Streptococcus* spp. (2 weeks), *S. aureus* (4 weeks IV minimum), or GN rods (4 weeks)
- surgical drainage if
 - persistent positive joint cultures on repeat arthrocentesis
 - hip joint involvement
 - prosthetic joint
- daily joint aspirations until culture sterile; no need to give intra-articular antibiotics
- physiotherapy

Prognosis

- gonococcal: responds well after 24-48 hours of initiating antibiotics (usually complete recovery)
- non-gonococcal: up to 50% morbidity (decreased joint function/mobility)

Diabetic Foot Infections

- neuropathic foot ulcers that can become infected:
 - mild = superficial (no bone/joint involvement)
 - moderate = deep (spread beneath superficial fascia) involving bone/joint
 - severe = moderate infection with systemic toxicity

Etiology

- mild: *S. aureus*, *Streptococcus* spp.
- moderate/severe: polymicrobial with aerobes (*S. aureus*, *Streptococcus*, *Enterococcus*, GN bacilli) and anaerobes (*Peptostreptococcus*, *Bacteroides*, *Clostridium*)

Clinical Features

- not all ulcers are infected
- infected ulcers are diagnosed on the basis of ≥ 2 of the cardinal signs of inflammation (redness, warmth, swelling, pain) or the presence of pus
- \pm crepitus, osteomyelitis, systemic toxicity

Investigations

- curettage specimen or bone biopsy (superficial swabs not useful)
- blood C&S
- assess for osteomyelitis by x-ray (although not sensitive in early stages)
 - if initial x-ray normal, repeat 2-4 wks after initiating treatment to increase test sensitivity
 - if initial x-ray equivocal, do MRI or bone biopsy (most reliable test)

Treatment

- evaluate for early surgical debridement \pm revascularization or amputation
- mild: TMP/SMX-DS 2 tabs PO BID + metronidazole 500 mg PO x 1-2 wks, longer if slow resolution
- moderate: ciprofloxacin 500 mg PO BID + clindamycin 300 mg QID x 2-4wks if no bony involvement, longer if viable, infected bone *in situ*
- severe: same as for "moderate" or imipenem or pip-tazo



Intra-articular steroids are contraindicated until septic arthritis has been excluded.

Does This Patient with Diabetes Have Osteomyelitis of the Lower Extremity?

JAMA 2008; 299(7): 806-13

Study: Systematic literature review. 21 studies.

Population: 1027 adult patients with diabetes mellitus being investigated for osteomyelitis.

Intervention: Various aspects of history, physical exam, laboratory tests, and diagnostic imaging studies versus bone biopsy.

Primary outcome: Diagnostic utility.

Results: No studies examined any part of history taking. Temperature, ulcer characteristics (erythema, swelling, purulence), elevated WBC, skin swabs, and soft tissue cultures were not useful. Nuclear imaging has poor specificity for osteomyelitis (62%-88.5%), and MRIs have greater accuracy in detecting osteomyelitis.

Finding	(+) LR	(-) LR
Visualization of bone	9.2	0.70
Ulcer area >2cm ²	7.2	0.48
Probe-to-bone	6.4	0.39
Clinical judgment	5.5	0.54
ESR >70mm/h	11	NS*
Plain radiographs	2.3	0.63
MRI	3.8	0.14

*NS- not significant

Osteomyelitis

- see Orthopaedics, OR8

Early Goal-Directed Therapy for Severe Sepsis and Septic Shock

NEJM 2001; 345:1368-77

Study: Randomized controlled trial with a 72 hour follow up.**Participants:** Patients presenting to emergency with severe sepsis or septic shock who met strict inclusion/exclusion criteria.**Intervention:** Patients received either 6 hours of early goal-directed therapy (n=130) or standard therapy (hemodynamic support protocol at the clinicians' discretion; n=133) prior to ICU admission.**Primary Outcome:** Mortality and APACHE II scores.**Results:** The mortality rate in the early therapy group was 30.5% compared to 46.5% receiving standard therapy (P=0.009). Within the 72 hours, early therapy resulted in a significantly higher mean central venous oxygen saturation (70.4% vs. 65.3%), a lower lactate concentration (3.0 vs. 3.9 mmol/L), and a higher pH (7.40 vs. 7.36) compared to standard therapy (P<0.02 for all comparisons). APACHE II scores were significantly lower in the early therapy group (13.0 vs. 15.9; P<0.001).**Conclusion:** Severe sepsis and septic shock significantly benefit from early goal-directed therapy compared to standard therapy protocols.

Systemic Infections

Sepsis and Septic Shock

Definitions

- systemic inflammatory response syndrome (SIRS): 2 or more of
 - (a) temperature <35°C or >38.5°C
 - (b) heart rate >90
 - (c) respiratory rate >20
 - (d) WBC <4 or >12
- sepsis: SIRS + documented infection
- septic shock: sepsis + hypotension, despite fluid resuscitation, and evidence of inadequate tissue perfusion, end-organ dysfunction and hypoperfusion

Pathophysiology

- bacteremia may or may not be present and may be primary (due to direct inoculation of blood, e.g. via indwelling catheter) or secondary (with extravascular focus of infection)
- circulatory insufficiency occurs when bacterial products interact with host cells and serum proteins to initiate a widespread and unregulated host response that ultimately leads to cell injury (both ischemic and directly cytopathic) and death
- septic shock develops in <50% of patients with bacteremia: ~40% of patients with Gram-negative bacteremia, ~20% of patients with *S. aureus* bacteremia

Clinical Features

- history: fever, chills, dyspnea, cool extremities, fatigue, malaise, anxiety, confusion
- physical: vitals (fever, tachypnea, tachycardia, hypotension), local signs of infection
- labs: CBC + diff, electrolytes, BUN, creatinine, liver enzymes, ABG, lactate, INR, PTT, FDP, blood cultures x3, urinalysis, urine C&S and cultures of any wounds or lines
- CXR (other imaging depends on suspicion of focus)

Treatment (also see Respirology, R35)

- respiratory supportive: O₂ ± intubation
- cardiovascular support: IV fluids, ± dopamine, ± norepinephrine; ICU transfer
- IV antibiotics (empirical, depends on suspected source)
- activated protein C
 - modulates coagulation and inflammation in severe sepsis
 - evidence suggests use in severe sepsis
 - contraindicated in patients at risk of significant bleeding complications
- IVIg: some evidence for Streptococcal Toxic Shock Syndrome but limited by small size of trials in literature
- hydrocortisone in patients with septic shock unresponsive to fluid resuscitation and vasopressors without risk stratification based on the ACTH stimulation test

Tuberculosis (TB)

Etiology, Epidemiology and Natural History

- Mycobacterium tuberculosis*: slow growing aerobe (doubling time = 18 h) that is capable of intracellular survival because it replicates in macrophages
- 5% of primary infections lead to progressive primary disease
- 95% of primary infections lead to latent TB
- 1/3 of the world's population is infected with latent TB
- 5-10% of those infected with latent TB experience reactivation disease, most often within the first 2 years of infection

Risk Factors

- for exposure/infection
 - travel or birth in country with high TB prevalence (e.g. Asia, Sub-Saharan Africa)
 - aboriginal, crowded living conditions, low SES/homeless
 - personal or occupational contact
- for progression from latent infection to active disease
 - immunocompromised/immunosuppressed (including extremes of age)
 - concurrent local disease process (i.e. pulmonary silicosis with latent pulmonary TB)
 - skin test conversion within past 2 years
 - iatrogenic – biologics (e.g. adalimumab, infliximab, etanercept), corticosteroids

Clinical Features

- primary infection usually asymptomatic, although progressive primary disease may occur, especially in children and immunosuppressed patients
- secondary infection/reactivation usually produces constitutional symptoms (fatigue, anorexia, night sweats, weight loss) and site-dependent symptoms

**Tuberculous Polyserositis**

= pleural + pericardial + peritoneal effusions
(usually from granuloma breakdown that spills TB into pleural cavity)

- i. pulmonary TB
 - chronic productive cough \pm hemoptysis
 - CXR consolidation or cavitation, lymphadenopathy
 - non-resolving pneumonia despite standard antimicrobial therapy
- ii. miliary TB
 - widely disseminated spread especially to lungs, abdominal organs, marrow, CNS
 - CXR: multiple small 2-4 mm millet seed-like lesions
- iii. extrapulmonary TB
 - lymphadenitis, pleurisy, pericarditis, hepatitis, peritonitis, meningitis, osteomyelitis (vertebral = Pott's disease), adrenal infection (causing Addison's disease), renal, ovary

Investigations

- PPD/Mantoux skin test: positive result only indicates infection, not active disease (PPD is not used to diagnose or exclude active TB)
- morning sputum on 3 consecutive days for acid fast bacilli (AFB), culture \pm AMTD (TB rRNA assay)
- CXR
 - nodular or alveolar infiltrates with cavitation (middle/lower lobe if primary, apical if secondary)
 - pleural effusion (usually unilateral and exudative) may occur independently of
 - pulmonary nodules
 - hilar/mediastinal adenopathy (especially in children)
 - tuberculoma (semi-calcified well-defined solitary coin lesion 0.5-4 cm that may be mistaken for lung CA) represents active or healed lesion
 - miliary TB: discrete nodules (2-4 mm diameter) scattered throughout lungs
 - evidence of past disease: calcified hilar and mediastinal nodes, calcified focus, pleural thickening with calcification, apical scarring
- interferon gamma release assay
 - in patients with TB, T-cells produce increased amounts of IFN γ when re-exposed to TB antigen
 - antigen not in the BCG vaccine or non-tuberculous mycobacteria (NTM), therefore fewer false positives
 - not currently recommended for routine screening, but may be useful in skin test positive patient with low pretest risk and history of BCG or NTM

Prevention

- prevention of infection: BCG (Bacille Calmette-Guérin) vaccine
 - ~80% effective against pediatric miliary and meningeal TB
 - effectiveness in adults debated (anywhere from 0-80%)
 - routine use rarely recommended in Canadian populations
- prevention of progression of latent to active disease (defer in pregnancy unless mother is high risk)
 - likely INH-sensitive: isoniazid (INH) 300 mg + pyridoxine (vit B₆) 50 mg PO OD x 9 mos
 - likely INH-resistant: rifampin 600 mg PO OD x 4 mos

Treatment of Active Infection

- empiric therapy: INH + rifampin + pyrazinamide + ethambutol + vitamin B₆
- pulmonary TB: INH + rifampin + pyrazinamide x 2 mos (initiation phase), then INH + rifampin x 4 mos (continuation phase), total 6 mos
- extrapulmonary TB: same regimen as pulmonary TB but increase to 12 mos in bone/joint, CNS, and miliary/disseminated TB + corticosteroids for meningitis, pericarditis
- empiric treatment of suspected MDR (multidrug resistant) or XDR (extensively drug-resistant) TB requires referral to a specialist
 - MDR = resistance to INH and RIF \pm others
 - XDR = resistance to INH + RIF + fluoroquinolone + ≥ 1 of injectable, second-line agents
 - suspect MDR TB if previous treatment, exposure to known MDR index case, or immigration from a high-risk area



Positive PPD Test

If induration at 48-72 h
 >5 mm if immunosuppressed, close contact with active TB, CXR fibrocalcific disease, with HIV-positive or if using anti-TNF blockers
 >10 mm all others; decision to treat depends on individual risk factors
False -: poor technique, anergy, malignancy, infection <10 wks ago or remotely
False +: BCG after 12 mos of age in a low-risk individual
Booster effect: initially false - result boost to a true + result by the testing procedure itself (usually if patient was infected long ago so had diminished delayed type hypersensitivity reaction or if history of BCG)
PPD: purified protein derivative



Treatment of Active TB

RIPE
 Rifampin
 Isoniazid
 Pyrazinamide
 Ethambutol

Leprosy (Hansen's Disease)

Etiology

- *Mycobacterium leprae*: obligate intracellular bacteria, slow-growing (doubling time 12.5 days), survives in macrophages
- transmission via respiratory droplets
- invades skin and peripheral nerves leading to chronic granulomatous disease

Clinical Features

- lesions involve cooler body tissues (e.g. skin, superficial nerves, nose, eyes, larynx)
- spectrum of disease determined by host immune response to infection
 - i. paucibacillary "tuberculoid" leprosy (intact cell-mediated immune response)
 - ≤ 5 hypoesthetic lesions, usually hypopigmented, well-defined, dry
 - early nerve involvement, enlarged peripheral nerves, neuritic pain
 - either self-limited or progresses to multibacillary "lepromatous" form

- ii. multibacillary "lepromatous" leprosy (low cell-mediated immune response)
 - ≥ 6 lesions, symmetrical distribution
 - leonine facies (loss of eyebrows, thickened ear lobes)
 - extensive cutaneous involvement, late and insidious nerve involvement
- iii. borderline leprosy
 - lesions and progression lies between tuberculoid and lepromatous forms

Investigations

- skin biopsy down to fat or slit skin smears for AFB (acid-fast staining, PCR)
- histologic appearance: intracellular bacilli in spherical masses (lepra cells), granulomas involving cutaneous nerves

Treatment (WHO Treatment Regimens)

- paucibacillary: dapsone 100 mg PO OD + rifampin 600 mg monthly x 6 months
- single skin lesion paucibacillary: single dose of rifampicin 600 mg, ofloxacin 400 mg, and minocycline 100 mg
- multibacillary and borderline: dapsone 100 mg PO OD + rifampin 600 mg monthly + clofazimine 300 mg PO monthly and 50 mg PO OD x 12 months
- reactional states (e.g. erythema nodosum leprosum and reversal reaction) may occur due to therapy: symptomatic if mild, prednisone 40-60 mg PO OD with 6-12 week taper if severe

Prognosis

- curable with WHO-approved treatment regimens
- complications: muscle atrophy, contractures, trauma/superinfection of lesions, crippling/loss of limbs, erythema nodosum leprosum
- long post-treatment follow-up warranted to monitor for relapse and 'reactions'



Argyll Robertson Pupil

Accommodates but does not react to light.



Those with Untreated 1° or 2° Syphilis

1/3 cure
1/3 latent indefinitely
1/3 3° syphilis



VDRL and RPR Test for Syphilis have a High False Positive Rate (up to 25% of all positive results)

Such false positive results can be caused by:

- Viruses (mono, hepatitis) and other active infections
- Drugs and substance abuse
- Connective tissue disease (e.g. SLE)
- Malignancy
- Pregnancy



Patients with 2° or 3° syphilis treated with penicillin may experience a Jarisch-Herxheimer reaction. Fever, chills, myalgia, flu-like symptoms may last up to 24 hours.



VDRL	Venereal Disease Research Laboratory
RPR	Rapid plasma reagin
EIA	Enzyme immunoassay
TPI	<i>T. pallidum</i> immobilization assay
FTA-ABS	Fluorescent <i>Treponema</i> Ab-absorption
MHA-TP	Microhemagglutination assay <i>T. pallidum</i>
TPPA	<i>T. pallidum</i> particle agglutination assay

Syphilis

Etiology

- *Treponema pallidum*: thick motile spirochetes detectable by dark-field microscopy historically, although rarely done now
- transmitted sexually, vertically, or parenterally (rare)

Clinical Features

- see Dermatology, D32 and Gynecology, GY28
- multi-stage disease
 - i. primary syphilis (3-90 days post-infection)
 - painless chancre at inoculation site (any mucosal surface)
 - regional lymphadenopathy
 - acute disease lasts 3-6 weeks, 25% progress to secondary syphilis without treatment
 - ii. secondary syphilis = systemic infection (2-8 weeks following chancre)
 - maculo-papular non-pruritic rash including palms and soles
 - generalized lymphadenopathy, low grade fever, malaise, headaches, aseptic meningitis, ocular/otic syphilis
 - condylomata lata: painless, wart-like lesion on palate, vulva or scrotum (highly infectious)
 - iii. latent syphilis
 - asymptomatic disease that occurs without treatment
 - early latent (<1 y post-infection) or late latent/unknown duration (>1 y post-infection)
 - increased transmission risk with early latent; longer treatment duration with late latent
 - iv. tertiary syphilis (1-30 y post-infection)
 - gummatous syphilis: nodular granulomas of skin, bone, liver, testes, brain
 - aortic aneurysms and valvular disease (AI)
 - neurosyphilis – dementia, personality changes, Argyll-Robertson pupils, tabes dorsalis
 - v. congenital syphilis
 - causes spontaneous abortions, stillbirths, congenital malformations, mental retardation, deafness
 - infants may be asymptomatic until age 2-5 then present with rhinitis, fever, lymphadenopathy, bone and cartilage degeneration (including saddle nose), hepatosplenomegaly, rash

Investigations

- screening tests: VDRL, RPR
- confirmatory tests: TPI, FTA-ABS, MHA-TP, TPPA, dark field microscopy with silver stain
- LP for 3° syphilis if: seropositive and symptoms of neurosyphilis or HIV negative with treatment failure/other tertiary symptoms/RPR $\geq 1:32$, or with HIV disease and late latent/unknown duration syphilis
- consider LP in all seropositive patients with HIV and CD4 <350, RPR >1:32

Treatment

- for 1°, 2°, latent <1 y: PenG 2.4 million units IM x 1; for 3°, latent (>1 y): benzathine PenG 2.4 million units IM weekly x 3, if allergic to penicillin: doxycycline 100 mg PO bid x 14 d
- neurosyphilis: aqueous PenG 18-24 million units/d IV x 10-14 d

Lyme Disease

Etiology/Epidemiology

- spirochete bacteria: *Borrelia burgdorferi* (N. America); *B. garinii*, *B. afzelii* (Europe and Asia)
- Lyme disease has been reported in 49 of the 50 U.S. states, but most cases occur in the Northeast, the Midwest, and Northern California
- reservoir: white-footed mouse (esp. BC's Fraser Delta + Vancouver Island; Ontario's north shore Lake Erie); white tailed deer
- transmitted by *Ixodes* tick
- human contact usually May-August in fields with low brush near wooded areas
- infection usually requires >36 h tick attachment

Clinical Features

- stage 1 (early localized stage: weeks post-infection)
 - malaise, fatigue, headache, myalgias
 - erythema chronicum migrans (ECM): expanding, non-pruritic bulls-eye (target) lesions (red with clear centre) on thigh/groin/axilla
- stage 2 (early disseminated stage: weeks to months post-infection)
 - CNS: aseptic meningitis, CN palsies (CN VII), peripheral neuritis
 - cardiac: transient heart block or myocarditis
- stage 3 (late persistent stage: months to years post-infection)
 - may not have preceding history of early stage infection
 - MSK: monoarticular or oligoarticular arthritis
 - acrodermatitis chronica atrophicans (due to *B. afzelii*)
 - neurologic: encephalopathy, meningitis, neuropathy



BAKE a Key Lyme Pie: Bell's palsy, Arthritis, Kardiak block, Erythema chronicum migrans

Investigations

- serology: ELISA, Western Blot

Prevention

- use of protective clothing, insect repellent, inspection for ticks and prompt removal of tick
- prophylaxis within 72 h of finding engorged attached nymphal tick in hyperendemic area (not routinely recommended): doxycycline 200 mg PO x 1 dose
- vaccine (Lymerix®): no longer available

Treatment

- stage 1: doxycycline 100 mg PO BID x 14-21 d or amoxicillin or cefuroxime
- stage 2-3: ceftriaxone 2 g IV q24h x 3-4 wks

Toxic Shock Syndrome (TSS)

Etiology

- superantigens produced by some strains of *S. aureus* or Group A *Streptococcus* cause widespread T-cell activation and cytokine release (IL-1, IL-6, TNF)
- Staphylococcal TSS: toxic shock syndrome toxin 1 (TSST-1)
- Streptococcal TSS: exotoxins SPEA, SPEB, SPEC

Risk Factors

- Staphylococcal: tampon use, nasal packing, wound infections
- Streptococcal: minor trauma, preceding viral illness (chickenpox), comorbid medical conditions

Clinical Features

- acute onset, fever, sBP <90 mmHg
- Staphylococcal TSS: involvement of 3 or more organ systems: GI (vomiting, watery diarrhea), muscular (myalgia, increased CK), mucous membranes (hyperemia), renal, hepatic, heme (thrombocytopenia), CNS (disorientation), rash with subsequent desquamation, especially on palms and soles
- Streptococcal TSS: ≥2 of coagulopathy, respiratory failure, soft tissue necrosis (necrotizing fasciitis, myositis, gangrene), liver or renal failure, erythematous macular rash

Treatment

- supportive: fluid resuscitation
- Staphylococcal: cloxacillin IV x 10-14 days
- Streptococcal: high-dose penicillin and clindamycin, IVIg

Important Exposures**Insect Bites**

Mosquito	<i>Plasmodium</i> spp. (Malaria) Dengue Lymphatic filariasis (Elephantiasis) West Nile Encephalitis Yellow Fever Japanese Encephalitis
Tick	<i>Borrelia burgdorferi</i> (Lyme Disease) <i>Rickettsia rickettsii</i> (Rocky Mountain Spotted Fever)
Fly	<i>Trypanosoma brucei</i> spp. (African sleeping sickness) <i>Leishmania</i> spp. (Leishmaniasis) <i>Bartonella bacilliformis</i> (Bartonellosis)
Flea	<i>Yersinia</i> (Plague) <i>Tunga penetrans</i> (Tungiasis)

Mammal Bites

Dog/Cat	Rabies, Pasteurella, anaerobes, <i>Streptococcus</i> , <i>S. aureus</i>
Human	<i>Streptococcus</i> , <i>S. aureus</i> , oral anaerobes

Oral Exposures

Unpasteurized Milk	<i>Brucella</i> spp., <i>Mycobacterium</i> spp., <i>Salmonella</i> , <i>E. coli</i> , <i>Listeria</i>
Undercooked Meat	Enteric bacteria, helminths, protozoa
Water	Hep A/E, Norwalk, cholera, <i>Salmonella</i> , <i>Shigella</i> , <i>Giardia</i> , poliovirus, <i>Cryptosporidium</i> , <i>Cyclospora</i>

Environmental Exposures

Freshwater	<i>Leptospira</i> spp., schistosomes, <i>Acanthamoeba</i> , <i>Naegleria fowleri</i>
Soil	Hookworms, <i>Toxocara</i> spp. (visceral larva migrans), <i>Leptospira interrogans</i> (leptospirosis)

Adapted with permission from Spira AM. Assessment of travellers who return home ill. *Lancet* 2003; 361(9367):1459-69

Cat Scratch Disease

Etiology

- *Bartonella henselae*: intracellular bacteria
- cat-to-human transmission via cat scratch/bite

Clinical Features

- skin lesion appears 3-10 days post-innoculation
- may be followed by fever, tender regional lymphadenopathy, hepatosplenomegaly, neurologic symptoms
- usually self-limited

Investigations

- serology, lymph node biopsy

Treatment

- supportive in most cases
- azithromycin x 10-14 days in patients with moderate-severe disease or immunocompromise

Rocky Mountain Spotted Fever

Etiology

- *Rickettsia rickettsii*: obligate intracellular Gram negative organism
- reservoir hosts: rodents, dogs
- vectors: Dermacentor ticks

Clinical Features

- usually occurs in summer following tick bite
- influenza-like prodrome: acute onset fever, headache, myalgia, nausea/vomiting, anorexia
- macular rash appearing on day 2-4 of fever
 - begins on wrists and ankles, then spreads centrally to arms/legs/trunk
 - involvement of palms and soles
 - occasionally "spotless"

Investigations

- serology (indirect fluorescent antibody test)

Treatment

- doxycycline, usually 5-7 day course

West Nile Virus

Epidemiology

- virus has been detected throughout the United States and much of southern Canada
- overall case-fatality rates in severe cases are ~10%

Transmission

- mostly from mosquitoes that have fed on infected birds (crows, blue jays)
- transplacental, blood products (rare), organ transplantation

Clinical Features

- most are asymptomatic
- most symptomatic cases are mild (West Nile fever)
- acute onset of headache, back pain, myalgia, anorexia
- maculopapular non-pruritic rash involving chest, back, arms
- severe complications: encephalitis, meningoencephalitis and acute flaccid paralysis (especially in those >60 years)

Investigations

- IgM antibody in serum or CSF (cross reactivity with Yellow Fever and Japanese encephalitis vaccines, Dengue Fever, St. Louis encephalitis); may not reflect current illness as IgM antibody can last for >6 months
- viral isolation or PCR from CSF, tissue, blood and fluids (all have low sensitivity)
- CSF: elevated lymphocytes and protein if neurologic disease

Treatment and Prevention

- supportive
- mosquito repellent (DEET), drain stagnant water, community mosquito control programs

HIV and AIDS

Epidemiology

Canadian Situation (Public Health Agency of Canada, 2007)

- 63,604 positive HIV tests reported to the Public Health Agency of Canada from 1985 – November 2007; estimated that 30% unaware of HIV positive status
- estimated 2800-5200 new infections were diagnosed in Canada in 2007; men who have sex with men account for 58% of cases, IV drug users 20%, heterosexual transmission 22%

Global Situation (WHO Global Summary of the HIV/AIDS Epidemic, December 2008)

- estimated 33.4 million people living with HIV/AIDS in 2008
- estimated 2.7 million newly infected in 2008
- estimated 2.0 million AIDS-related deaths in 2008



HIV-1 is the predominant type in North America and most of the world.

HIV-2 is found mainly in West Africa.

Both lead to AIDS but HIV-2 is generally less virulent.

Pathophysiology

- HIV virion includes envelope (with gp41 and gp120 glycoproteins), matrix (with protein p17 and capsid (with protein p24) enclosing 2 single-stranded copies of RNA + enzymes in its core
- virion glycoproteins bind CD4 and CXCR4/CCR5 on T-helper cells to fuse and enter
- RNA converted to dsDNA by reverse transcriptase and integrated into host genome
- virus DNA transcribed during host replication and new virions are produced
- virions bud out of host cell, incorporating host cell membrane
- this process destroys the T-helper cells

Modes of Transmission

Table 18. Modes of Transmission by Site and Medium

HIV Invasion Site	Sub-location	Transmission Medium	Transmission Probability per Exposure Event
Female genital tract	Vagina, ectocervix, endocervix	Semen	1 in 200 to 1 in 2000
Male genital tract	Inner foreskin, penile urethra	Cervicovaginal and rectal secretions and desquamations	1 in 700 to 1 in 3000
Intestinal tract	Rectum Upper GI tract	Semen	1 in 20 to 1 in 300
		Semen	1 in 2500
		Maternal blood/genital secretions (intrapartum)	1 in 5 to 1 in 10
		Breastmilk	1 in 5 to 1 in 10
Placenta	Chorionic villi	Maternal blood (intrauterine)	1 in 10 to 1 in 20
Blood stream		Blood products/sharps	95 in 100 to 1 in 150

Adapted with permission from Macmillan Publishers Ltd. *Nat Rev Immunology* 2008;8:447-457.



Infection is NOT transmitted by casual contact, kissing, mosquitoes, toilet seats, shared utensils.



For recently exposed individuals (during window period), diagnosis can be made by DNA PCR or p24 antigen; a repeat ELISA test at 6 weeks and 3 months is indicated.

Laboratory Diagnosis

- seroconversion in 2-8 weeks; rare for antibodies to be undetectable after 3 months
- initial enzyme linked immunosorbent assay (ELISA) detects serum antibody to HIV; sensitivity >99.5%
- if positive test: Western blot confirmation by detection of antibodies to at least two different HIV protein bands (p24, gp41, gp120/160) specificity >99.99%
- rapid test: higher false positives, therefore need to confirm with Western blot
- PCR: detects HIV DNA in plasma for diagnosis and HIV RNA in plasma for monitoring viral load
- p24 antigen detection by ELISA; only positive in acute phase and late symptomatic stages



All infants born to HIV infected mothers have positive ELISA tests because of circulating maternal anti-HIV antibodies which disappear by 18 months; early diagnosis is made by detection of HIV RNA in plasma.

Natural History

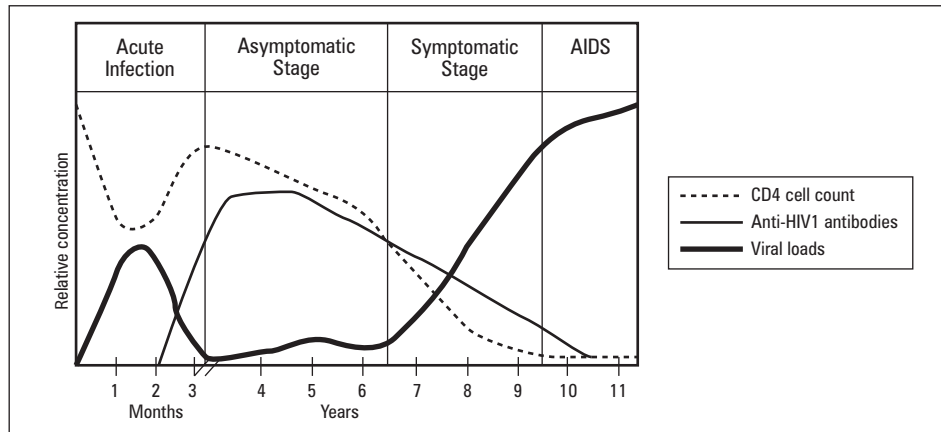


Figure 6. Relationships between CD4 T cell Count, Viral Load, and Anti-HIV Antibodies



AIDS Definition

HIV-positive, OR
CD4 <14% of all lymphocytes, OR
One or more AIDS-defining illnesses

Acute Retroviral Syndrome

- experienced in 40-70% 1-6 weeks post-exposure lasting 10-15 days
- symptoms include fever, pharyngitis, lymphadenopathy, rash, myalgias, headaches, leukopenia
- 10-20% present with aseptic meningitis; HIV RNA and/or p24 may be detected in CSF
- associated with high level plasma viremia and therefore high risk of transmission

Asymptomatic Phase

- by 10 years post-infection, 50% have AIDS, 30% demonstrate milder symptoms and <20% are asymptomatic if left untreated
- CD4 counts usually greater than 200 cells/mm³
- persistent generalized lymphadenopathy occurs in 35-60% of asymptomatic patients

Table 19. Symptomatic Phase

CD4 counts	Possible Manifestations
<500 cells/mm ³	Constitutional symptoms: fever, night sweats, fatigue, weight loss Mucocutaneous lesions: seborrheic dermatitis, HSV, VZV (shingles), oral hairy leukoplakia (EBV), candidiasis (oral, esophageal, vaginal), Kaposi's sarcoma (KS) Recurrent bacterial infections, especially pneumonia Pulmonary and extrapulmonary tuberculosis Lymphoma
<200 cells/mm ³	<i>Pneumocystis jiroveci</i> pneumonia (formerly PCP) Visceral KS Oral thrush Local and/or disseminated fungal infections: <i>Cryptococcus neoformans</i> , <i>Coccidioides immitis</i> , <i>Histoplasma capsulatum</i>
<100 cells/mm ³	Progressive multifocal leukoencephalopathy (PML) – JC virus CNS toxoplasmosis
<50 cells/mm ³	CMV infection: retinitis, colitis, cholangiopathy, CNS disease Mycobacterium avium complex (MAC) Bacillary angiomatosis (disseminated <i>Bartonella</i>) Primary central nervous system lymphoma (PCNSL), Acquired Immunodeficiency Syndrome (AIDS)

AIDS surveillance definition in Canada:

HIV-positive, AND one or more clinical illnesses that characterize AIDS, including: opportunistic infections (e.g. PCP, esophageal candidiasis, CMV, MAC, TB, toxoplasmosis) malignancy (Kaposi's sarcoma, invasive cervical cancer) wasting syndrome

Management of the HIV-Positive Patient



Encourage safer sex, even with other HIV-positive individuals, to decrease risk of comorbid STIs and to prevent spread of HIV resistance.

- verify that there is a positive HIV test
- complete baseline history and physical examination, then follow-up every 3 months
- physical exam
 - optic fundi for hemorrhagic lesions characteristic of CMV retinitis
 - oral cavity for lesions
 - lymph node enlargement
 - hepatosplenomegaly
 - genital lesions
 - neurological exam for peripheral neuropathy, decreased global cognition

- education
 - regular follow-up on CD4 counts and viral loads as well as strict compliance on ARVs improves prognosis
 - prevention of further transmission through safer sex and clean needles for drug use
 - different viral genotypes can transfer resistance patterns between 2 HIV+ people so barrier protection during sex is still important
- laboratory evaluation
 - baseline plasma HIV-RNA level and CD4 count, repeat with CBC and differential every 3-4 months
 - baseline HIV resistance testing
 - baseline tuberculin skin test (PPD): induration greater than 5 mm is positive
 - baseline *Toxoplasma* antibody, syphilis serology, hepatitis A, B and C serologies, CMV antibody, VZV serology, and CXR
 - ◆ basic chemistry, liver enzymes, bilirubin every 3-6 months
 - ◆ annual fasting lipid profile and fasting glucose
- health care maintenance
 - assessment for ongoing counseling needs and referral for significant psychiatric or social problems
 - vaccines: influenza annually, 23-valent pneumococcal every 5 years, hepatitis B (if not immune), hepatitis A (if seronegative)
 - annual PAP smear
 - assessment and management of comorbid conditions (e.g. blood pressure monitoring, smoking cessation, alcohol/drug use, safer sex)



1° and 2° prophylaxis may be discontinued if CD4 count is above threshold for ≥6 months while on HAART.



Reasons for Deterioration of a Patient with HIV/AIDS

Opportunistic infections
Neoplasms
Medication-related toxicities
Co-infections (e.g. HBV, HCV, STIs)
Non-AIDS-related comorbidities (e.g. cardiovascular, renal, hepatic, neurocognitive, bone disease)

Table 20. Prophylaxis Against Opportunistic Infections in HIV-infected Patients

Pathogen	Indication for Prophylaxis	Prophylactic Regimen
<i>Pneumocystis jirovecii</i> (see ID36)	CD4 count <200 cells/mm ³ or history of oral candidiasis	TMP-SMX 1 SS or DS OD
<i>Toxoplasma gondii</i>	IgG antibody to <i>Toxoplasma</i> and CD4 count <100 cells/mm ³	TMP-SMX 1 DS OD
<i>Mycobacterium tuberculosis</i>	PPD reaction >5 mm or contact with case of active TB	Isoniazid + pyridoxine x 9 months
<i>Mycobacterium avium</i> complex	CD4 count <50 cells/mm ³	Azithromycin 1200 mg q week or Clarithromycin 500 mg BID
Varicella zoster virus	Exposure to chicken pox/shingles in previously unexposed	VZIG within <96 hrs of exposure

SS = single strength, DS = double strength

See 2002 USPHS/IDSA Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons. <http://aidsinfo.nih.gov/>

Highly Active Antiretroviral Treatment (HAART)

Overall Treatment Principles

- initiate HAART when CD4=350; ongoing debate about when to initiate HAART when CD4 is between 350-500 or >500
- consider results of baseline resistance testing and complete ARV treatment history before initiating HAART
- **goal:** keep viral load <50 copies/ml (high viral load is defined as >100 000 copies/ml)
 - viral load should decrease 3-4 fold within 2-8 weeks; undetectable by 6 mos
- **goal:** restore immunological function
- joint patient-physician decision for treatment considerations
- improve quality of life and treat/minimize drug side effects
- if the patient is also coinfecting with hepatitis C then start treatment early

HAART Recommendations for Treatment of Naïve Patients

- NNRTI + 2 NRTIs (see Table 22) OR
- PI (boosted with ritonavir) + 2 NRTIs OR
- INSTI + 2 NRTIs

Treatment Failure

- defined clinically (HIV progression), immunologically (failure to increase CD4 count by 25-50 over first year of treatment or CD4 decrease), or virologically (failure to achieve viral load <400 copies/mL after 24 wks or <50 copies/mL after 48 wks)
- ensure that viral load >50 is not just a transient viremia or 'blip'



Treatment Failure

- Assess adherence
- Resistance testing
- Rule out opportunistic infections
- Rule out marrow suppression
- Construct new 3-drug regimen

**Lactic Acidosis**

Occurs secondary to mitochondrial toxicity.

Symptoms include abdominal pain, fatigue, N/V, muscle weakness.

**Lipodystrophy**

Body fat redistribution:

Lipohypertrophy (e.g. dorsal fat pad, breast enlargement, increased abdominal girth) thought to be caused primarily by protease inhibitors
Lipoatrophy (e.g. facial thinning, decreased adipose tissue in the extremities) is thought to be caused by thymidine analogue NRTIs such as d4T and AZT.

Metabolic abnormalities: lipids (increase LDL, increase TGs), glucose (insulin resistance, DM2), increase risk CVD

**Ritonavir-boosting for Protease Inhibitors**

- Ritonavir inhibits the metabolism of other PIs by inhibiting cytochrome P450 3A4 and p-glycoprotein, the enzyme systems responsible for metabolism of the PIs
- The goal of PI boosting is to increase the plasma exposure to PIs
- PI boosting is best achieved by administering low-dose ritonavir along with the PI

**HLA-B*5701 testing**

Abacavir hypersensitivity reactions usually only occur in individuals carrying this HLA allele (~5-7% of Caucasians, lower prevalence in other ethnic groups). Routine screening for HLA-B*5701 prior to abacavir use.

**Tropism testing**

In addition to CD4, HIV requires a co-receptor (either CCR5 or CXCR4) to enter cells.
CCR5 antagonists (eg. Maraviroc) only work if virus is CCR5-tropic.
Tropism test required prior to initiating CCR5 antagonists.

Table 21. Guidelines for Initiating Antiretroviral Therapy in Chronically HIV-infected Patients

Clinical Category	Laboratory Category	Recommendation
AIDS-defining illness or severe symptoms of HIV infection	Any CD4 count	Treat
Asymptomatic	CD4 \leq 350 cells/mm ³	Treat
Asymptomatic	CD4 > 350 cells/mm ³	Consider treatment to decrease risk of HIV-associated complications (e.g. TB, Kaposi's), decreased HIV transmission to others
HIV-associated nephropathy	Any CD4 count	Treat
HIV-associated thrombocytopenia	Any CD4 count	Treat
Pregnant women	Any CD4 count	Treat to prevent mother-child transmission. Consider discontinuing treatment post-partum if not otherwise indicated
Persons co-infected with hepatitis B virus (HBV), when HBV treatment is indicated	Any CD4 count	Treat both HIV and HB

See 2008 OARAC Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>

Table 22. Antiretroviral Drugs

Class	Drugs	Mechanism	Adverse Effects
Nucleoside reverse transcriptase inhibitors (NRTIs)	zidovudine (AZT) lamivudine (3TC) stavudine (d4T) didanosine (ddI) abacavir (ABC) emtricitabine (FTC) Combo Tablets: AZT/3TC (Combivir®) AZT/3TC/ABC (Trizivir®) ABC/3TC (Kivexa®) TDF/FTC (Truvada®)	Incorporated into the growing viral DNA chain, thereby competitively inhibiting reverse transcriptase and terminating viral DNA growth	Lactic acidosis Lipodystrophy Rash N/V/diarrhea Bone marrow suppression (AZT) Peripheral neuropathy (ddI, d4T) Drug-induced hypersensitivity (ABC) Pancreatitis (ddI/d4T) Myopathy (AZT)
Nucleotide reverse transcriptase inhibitors	tenofovir (TDF)	Similar to NRTIs, except are chemically preactivated and thus require less biochemical processing in the body to become active	Renal dysfunction N/V/diarrhea
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	efavirenz nevirapine (NVP) delavirdine (DLV) etravirine	Non-competitively inhibit function of reverse transcriptase, thereby preventing viral RNA replication	Rash, Stevens-Johnson syndrome CNS: dizziness, insomnia, somnolence, abnormal dreams (efavirenz) Hepatotoxicity (nevirapine – avoid in females with CD4 > 250, men with CD4 > 400) CYP3A4 interactions
Protease inhibitors (PIs)	ritonavir saquinavir amprenavir (APV) nelfinavir indinavir atazanavir fosamprenavir lopinavir/ritonavir (Kaletra®) tipranavir darunavir	Prevent maturation of infectious virions by inhibiting the cleavage of polyproteins	Lipodystrophy, metabolic syndrome N/V/diarrhea Nephrolithiasis (indinavir) Rash (APV) Hyperbilirubinemia (ataz, indinavir) CYP3A4 interactions Hyperlipidemia
Fusion inhibitor	enfuvirtide (T-20)	Inhibit viral fusion with T-cells by inhibiting gp41, preventing cell infection	Injection site reactions, rash, infection, diarrhea, nausea, fatigue
CCR5 antagonist	maraviroc	Inhibit viral entry by blocking host CCR5 co-receptor	Fever, cough, dizziness
Integrase strand transfer inhibitors (INSTIs)	raltegravir elvitegravir	Inhibits integration of HIV DNA into the human genome thus preventing HIV replication	

Standard of care is to boost most PIs with ritonavir for maximal pharmacokinetic properties.

Prevention of HIV Infection

- education, including harm-reduction:
 - safer sexual practices: condoms for vaginal and anal sex, barriers for oral sex
 - harm prevention for IV drug users: avoid sharing needles
- treatment of HIV+ women with HAART during the 2nd and 3rd trimester of pregnancy and AZT during delivery followed by AZT treatment of the infant for 6 weeks (decreases maternal-fetal transmission from 25% to <3%)
- universal blood and body precautions for health care workers
 - counselling and prophylaxis after occupational exposure with a PI-based regimen initiated immediately (<72 h) after exposure and continuing for 4 weeks
- screening of blood and organ donation

Types of Testing

1. Nominal/name-based HIV testing

- the person ordering the test knows the identity of the person being tested for HIV
- the HIV test is ordered using the name of the person being tested
- there is collection of patient identifying information, information detailing the HIV-related risk factors of the person being tested, and laboratory data
- person ordering the test is legally obligated to notify Public Health officials if test results are positive for HIV
- the test result is recorded in the health care record of the person being tested

2. Non-nominal/non-identifying HIV testing

- similar to nominal/name-based testing on all points except:
 - the HIV test is ordered using a code or the initials of the person being tested

3. Anonymous testing

- available at specialized clinics, organized and supported by public health departments, and by some health care providers
- the person ordering the HIV test does not know the identity of the person being tested for HIV
- the HIV test is carried out using a unique non-identifying code that only the person being tested for HIV knows
- data such as age, gender, HIV-related risk factors and the ethnicity of the person being tested for HIV may be collected during anonymous testing, depending on the site
- test results are not recorded on the health care record of the person being tested unless they subsequently decide to identify themselves for that purpose

Universal Routine Screening: A Novel Guideline in Primary Care

- new literature suggesting universal screening is cost effective
- 10% to 25% of people testing positive report no high-risk behaviors, which suggests an important limitation of risk based screening
- even when risk factors are in the medical record only 1/3 are tested for HIV
- some studies suggest that most persons who are aware of their HIV infection substantially reduce risky behaviors
- the CDC and Prevention and the U.S. Preventive Services Task Force (USPSTF) Guidelines recommend routine screening in all health care settings ages 13-64 unless the HIV prevalence of population is <0.1%

HIV Pre- and Post-test Counselling

- a diagnosis of HIV can be overwhelming and often includes social consequences such as stigma and discrimination
- counselling should be given pre-HIV test and after, regardless of the results
- goals include: assessing risk, making informed decision to be tested, education to protect themselves and others from virus-exposure, where to go for more information and support
- for positive tests, patients should get connected with local support services



Early identification of HIV is essential for patients to receive the maximum benefit from antiretroviral therapy.

Fungal Infections

Skin and Subcutaneous Infections

Superficial Fungal Infections

Clinical Features

- benign skin pigmentation changes
 - pityriasis versicolor (previously called *tinea versicolor*): hypo/hyperpigmented skin patches (will not darken in sun) caused by yeasts that are part of normal skin flora
 - tinea nigra: dark brown-black painless patches on soles of feet and palms

Treatment

- dandruff shampoo with selenium sulfide (Selsun®) applied to skin
- topical clotrimazole or ketoconazole (Nizoral®)
- oral ketoconazole or itraconazole

Dermatophytes

Definition

- refers to infection of keratinized tissues (in cutaneous skin layer) caused by three genera of molds
 - trichophyton infects skin, nails and hair
 - microsporum infects skin and hair
 - epidermophyton infects skin and nails

Pathophysiology

- fungi secrete keratinase (thus destroying the main structural protein of skin, nails, hair) resulting in scaling of skin, loss of hair and crumbling of nails

Transmission

- most dermatophytes are highly contagious and many can be spread by person-to-person contact

Clinical Features

- tinea barbae (“barber’s itch”)
 - colonization of bearded areas of face and neck in males
 - lesions range from erythematous perifollicular papules and pustules to nodular, abscess-like lesions with associated alopecia
- tinea capitis
 - infection of scalp which leads to scaling and non-scarring alopecia
 - usually occurs between 4-14 years of age
 - can also involve eyebrows and eyelashes
- tinea corporis (“ring worm”)
 - infection of hairless skin, can involve any area of skin
 - annular scaling plaque with erythematous border (area of inflammation) and central clearing (area of healing)
- tinea cruris (“jock itch”)
 - sharply demarcated lesions with erythematous margins and scaling
 - usually involves genitocrural area and upper medial thigh symmetrically
 - scrotum usually not involved (unlike candidal infection)
- tinea pedis (“athlete’s foot”)
 - infection of feet, usually involves webspace and soles
 - associated with occlusive shoes (provides warm and moist environment needed for fungal growth) and contact with public bath or pool floors
- tinea unguium (onychomycosis)
 - thick, discoloured, brittle nails
 - confirm by KOH microscopy, culture, or histologic examination

Treatment

- topical midazoles for mild cases of tinea corporis, tinea cruris, and tinea pedis (e.g. clotrimazole, miconazole)
- oral antifungals for tinea barbae, tinea capitis and tinea unguium (e.g. terbinafine)

Subcutaneous Fungal Infection

Pathophysiology

- fungi that naturally reside in soil and enter skin via traumatic break
- *Sporothrix schenckii*: most commonly affects gardeners injured by a rose thorn or splinter
 - causes subcutaneous nodule at point of entry
 - fungi may migrate up lymphatic vessels creating nodules along the way – “nodular lymphangitis”

Treatment

- oral itraconazole
- amphotericin B for severe or disseminated infection

Systemic/Endemic Mycoses

Basics

- three major systemic mycoses
 - histoplasmosis
 - blastomycosis
 - coccidioidomycosis
- thermally dimorphic organisms
- infection occurs through inhalation of spores (soil, bird droppings, vegetation) or inoculation injury, not human-to-human spread
- 95% of infections are asymptomatic or cause acute self-limited pneumonia
- remaining 5% become chronic pneumonia or disseminate hematogenously
- may reactivate or disseminate during immunocompromise

Histoplasma capsulatum

Endemic Region

- river valleys in central USA, Ontario, Quebec; widespread

Clinical Features

- primary pulmonary
 - fever, cough, chest pain, headache, myalgia, anorexia
 - CXR (acute): pulmonary infiltrates ± hilar lymphadenopathy
 - CXR (chronic): pulmonary infiltrates, cavitary disease
- disseminated
 - spread to bone marrow (pancytopenia), GI tract (ulcers), lymph nodes (lymphadenitis), skin, liver, adrenals, CNS

Investigations

- fungal culture, fungal stain
- antigen detection (urine + serum)

Treatment

- amphotericin B, itraconazole (if progressive lung involvement)



Histoplasmosis is commonly associated with exposure to chicken coops, bird roosts and bat caves.

Blastomyces dermatitidis

Endemic Region

- river valleys in midwest USA, Northern Ontario; not restricted to Northern Ontario

Clinical Features

- primary
 - fever, cough, chest pain, chills, night sweats, weight loss
 - CXR (acute): lobar pneumonia
 - CXR (chronic): lobar infiltrates, fibronodular interstitial disease
- disseminated
 - spread to skin (verrucous lesions that mimic skin cancer, ulcers, subcutaneous nodules), bones (osteolytic lesions), GU tract (prostatitis, epididymitis)

Treatment

- amphotericin B for severe disease
- itraconazole or voriconazole for mild-moderate disease

**High Risk for Dissemination**

1. Immunocompromised (e.g. AIDS, steroids, TNF- α inhibitors)
2. Pregnancy (3rd trimester)
3. Diabetes



The classic exposure risk for coccidioides is a trip to Arizona.

Coccidioides immitis

Endemic Region

- deserts in southwest USA, northwest Mexico

Clinical Features

- primary
 - “Valley fever”: subacute fever, chills, cough, chest pain, sore throat, fatigue that lasts for weeks to months
 - can develop hypersensitivity with arthralgias, erythema nodosum
- disseminated
 - rare spread to skin (ulcers), joints (synovitis), bones (lytic lesions), meninges (meningitis)

Treatment

- amphotericin B for severe disease
- itraconazole or fluconazole for mild-moderate disease

Opportunistic Fungi

***Pneumocystis jiroveci* (formerly *P. carinii*)**

Microbiology

- unicellular fungi
- previously classified as a protozoa

Transmission

- rarely person-to-person transmission
- most disease is due to reactivation of latent infection acquired by the respiratory route or reinfection by a different genotype
- common opportunistic infection in patients with HIV
 - increased disease when CD4 count $<200 \times 10^6/L$
 - 80% lifetime risk without prophylaxis in patients with CD4 count $<200 \times 10^6/L$

Clinical Features

- fever, nonproductive cough, progressive dyspnea
- classic CXR = diffuse interstitial infiltrate, starts perihilar (98% bilateral)
- CXR may be normal (20-30%)

Investigations

- sputum induction, bronchoalveolar lavage, endotracheal aspirate (if intubated), immunofluorescent staining

Treatment and Prevention

- oxygen to keep $SaO_2 >90\%$
- antimicrobial options:
 - TMP/SMX (PO or IV)
 - dapsone and TMP
 - clindamycin and primaquine
 - pentamidine (IV)
 - atovaquone
- corticosteroids used as adjuvant therapy in those with severe hypoxia ($pO_2 <70\text{mmHg}$ or A-a gradient $O_2 >35\text{ mmHg}$)
- prophylactic TMP/SMX for those at risk (primary if CD4 $<200 \times 10^6/L$, secondary prophylaxis for all patients with prior PCP until immune recovery)

***Cryptococcus* spp.**

Microbiology

- encapsulated yeast
- 4 serotypes: *C. grubii* (serotype A), *C. gattii* (serotypes B and C), *C. neoformans* (serotype D)

Transmission

- inhalation of airborne yeast from soil contaminated with pigeon droppings
- *C. neoformans* tends to affect immunocompromised hosts
- *C. gattii* tends to affect immunocompetent hosts



CXR in *P. jiroveci* may show anything including normal, but almost never pleural effusions.

Clinical Features

- pulmonary
 - usually asymptomatic or self-limited pneumonitis
- disseminated
 - CNS: meningitis (leading cause of meningitis in patients with HIV)
 - skin: lesions that resemble large molluscum contagiosum

Investigations

- serum cryptococcal antigen
- CSF for meningitis: India-ink stain, cryptococcal antigen test, culture to confirm
- blood C&S, urine C&S in men

Treatment

- amphotericin B (+ flucytosine) is first-line; induction therapy x 2 weeks
- fluconazole for consolidation therapy and maintenance therapy in HIV



India-ink sensitivity for cryptococcus is only 50% (higher in HIV patients).

Candida albicans

Microbiology

- yeast forms with pseudohyphae

Transmission

- normal flora of skin, mouth, vagina and GI tract
- risk factors: immunocompromised state, broad-spectrum antibiotics, diabetes, corticosteroids, central venous catheters, TPN

Clinical Features

- mucocutaneous
 - oral thrush, esophagitis (chest pain, odynophagia), vulvovaginitis (see [Gynecology](#), GY24), cutaneous (diaper rash, skin folds, folliculitis), chronic mucocutaneous
- invasive
 - candidemia, endophthalmitis, endocarditis, UTI (upper tract), hepatosplenic disease

Treatment

- thrush: swish and swallow nystatin, nystatin pastilles, single dose fluconazole
- vulvovaginal candidiasis: topical imidazole or nystatin, oral fluconazole
- cutaneous infection: topical imidazole
- AIDS/opportunistic infections (thrush, esophageal, vaginal): fluconazole, itraconazole, amphotericin B, echinocandins
- systemic: amphotericin B, fluconazole, echinocandins, voriconazole
- chronic mucocutaneous: fluconazole, itraconazole, posaconazole or amphotericin B

Aspergillus spp.

Microbiology

- branching septate hyphae
- common species causing disease include *A. fumigatus*, *A. flavus*

Transmission

- ubiquitous in environment (everywhere in air)
- *Aspergillus* produces a toxin called aflatoxin which contaminates nuts, grains and rice

Clinical Features

- allergic bronchopulmonary aspergillosis (ABPA)
 - IgE-mediated asthma-type reaction with dyspnea, high fever and transient pulmonary infiltrates
 - occurs more frequently in patients with asthma and allergies
- aspergilloma (fungus ball)
 - ball of hyphae in a preexisting lung cavity
 - ranges from asymptomatic to massive hemoptysis
 - CXR: round opacity surrounded by a thin lucent rim of air, often in upper lobes ("air crescent" sign)
- invasive aspergillosis
 - associated with prolonged and persistent neutropenia
 - pneumonia – most common
 - may disseminate to other organs: brain, skin
 - severe symptoms with fever, cough, dyspnea, pleuritic pain, tends to cavitate; fatal if not treated early and aggressively
 - CXR: local or diffuse infiltrates ± pulmonary infarction, pulmonary nodules

- mycotoxicosis
 - aflatoxin produced by *A. flavus* (nuts, grains, rice)
 - results in liver hemorrhage, necrosis and hepatoma formation

Treatment Options

- voriconazole, itraconazole, posaconazole, amphotericin B, caspofungin
- surgical resection for aspergilloma and hemorrhage
- steroids for allergic bronchopulmonary aspergillosis

Parasitic Infections

Entamoeba histolytica (Amoebas)

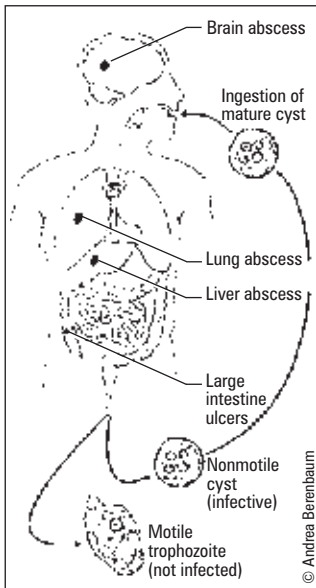


Figure 7. *Entamoeba* Life Cycle

Transmission

- reservoir: infected humans
- fecal-oral and food/waterborne transmission of cysts in areas of poor sanitation
- seen in immigrants, travellers, institutionalized individuals, Aboriginal Canadians, men who have sex with men (MSM)

Clinical Features

- asymptomatic carriers
- amoebic dysentery
 - abdominal pain, cramping, colitis, dysentery, low grade fever with bloody diarrhea secondary to local tissue destruction and ulceration of large intestine
- amoebic abscesses
 - most common in liver (hematologic spread); presents with RUQ pain, weight loss, fever, hepatomegaly
 - can also occur in lungs and brain

Investigations

- serology, fecal/serum antigen testing, stool exam (for cysts and trophozoites), colon biopsy
- *E. histolytica* indistinguishable microscopically from the non-pathogen *E. dispar* (distinguish by specific stool antigen detection)

Treatment and Prevention

- metronidazole
- for invasive disease or cyst elimination: follow with iodoquinol or paromomycin
- aspiration of hepatic abscess if risk of cyst rupture, poor response to medical therapy diagnostic uncertainty
- cyst/trophozoite passer: iodoquinol or paromomycin alone
- good personal hygiene, purification of water supply by boiling, filtration; not chlorination

Flagellates

Giardia lamblia

Transmission

- reservoir is infected humans and other mammals
- food/waterborne transmission (especially in the Rockies) and fecal-oral transmission of infectious cysts
- risk factors: institutions, daycare centres, MSM, travel, camping

Clinical Features

- giardiasis ("beaver fever")
 - symptoms vary from asymptomatic to mild watery diarrhea to malabsorption syndrome (parasite coats small intestine and thus prevents fat absorption)
 - nausea, malaise, abdominal cramps, bloating, flatulence, fatigue, weight loss, steatorrhea
 - no hematochezia (no invasion into intestinal wall), no mucus in stool

Investigations

- multiple stool samples (daily x 3 days) for microscopy, stool antigen used occasionally
- occasionally small bowel aspirate or biopsy

Treatment and Prevention

- metronidazole, nitazoxanide
- good personal hygiene and sanitation, water purification (iodine better than chlorination)

Trichomonas vaginalis

Transmission

- sexual, fomites

Clinical Features

- males often asymptomatic; occasionally urethritis, prostatitis
- trichomonas vaginitis (see *Gynecology*, GY25)
 - malodorous (fishy) yellow-green or grey, frothy vaginal discharge, dysuria, dyspareunia

Investigations

- wet mount (motile parasites), antigen detection, culture
- urine PCR to detect in males

Treatment

- metronidazole to patient and partner



Trichomonas causes 25% of vaginitis.

Trypanosoma cruzi

Transmission

- found in Mexico, South America and Central America
- transmission from *Reduviid* insect vector which defecate on skin and trypomastigotes in the stool penetrate skin (majority of infections)
- placental transfer, organ donation, blood transfusion and ingestion of contaminated food (especially cane juice)

Clinical Features

- American trypanosomiasis (Chagas' disease)
 - acute: usually asymptomatic, local swelling at site of inoculation (usually around one eye) with variable fever, lymphadenopathy, cardiomegaly and hepatosplenomegaly
 - intermediate phase: asymptomatic but increasing levels of parasite and antibody in blood; most infected persons remain in this phase
 - chronic: can lead to chronic dilated cardiomyopathy, esophagomegaly and megacolon 10-25 years after acute infection in 30-40% of infected individuals
- diagnosis: wet prep and Giemsa stain of thick and thin smear of blood, serology, PCR

Treatment and Prevention

- acute: nifurtimox or benznidazole
- intermediate: increasing trend to treat as acute
- chronic: symptomatic therapy, surgery including heart transplant as necessary, may be a benefit to antiparasitic treatment
- insect control, bed nets

Apicomplexa

***Cryptosporidium* spp.**

Transmission

- reservoir: infected humans and a wide variety of young animals
- fecal-oral transmission by ingestion of cysts, waterborne
- risk factors: summer and fall, young children (daycare), MSM, contact with farm animals, immunocompromise, immune reconstitution

Clinical Features

- cryptosporidiosis
 - symptoms range from self-limited watery diarrhea (immunocompetent) to chronic, severe, nonbloody diarrhea with nausea, vomiting, abdominal pain, and anorexia (immunocompromised) resulting in weight loss and death
 - 7-10 day incubation period

Investigations

- modified acid-fast stain of stool specimen, microscopic identification of oocysts in stool or tissue, stool antigen detection by direct fluorescent antibody (DFA)



Malaria is the most common fatal infectious disease worldwide.

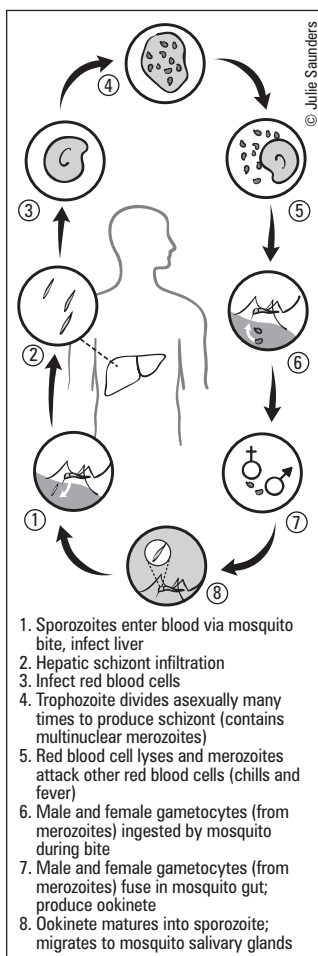


Figure 8. Life Cycle of *Plasmodium* spp.

Drugs for Preventing Malaria in Travelers

Cochrane Database Syst Rev 2009; 9: CD006491

Study: Cochrane Systematic Review. 8 RCTs.

Population: 4240 non-immune adult and children traveling to regions with *P. falciparum* resistance to chloroquine.

Intervention: Atovaquone-proguanil, doxycycline, mefloquine, chloroquine-proguanil, or primaquine used for malaria prophylaxis.

Outcome: Efficacy, safety, and tolerability.

Results: No evidence to use primaquine in malaria prophylaxis and limited evidence comparing and determining most effective drug. No serious adverse events reported in any trial (mortality). For common adverse events: Chloroquine-proguanil had more any adverse effect and adverse GI effects compared to doxycycline, atovaquone-proguanil, and mefloquine; Atovaquone-proguanil had fewer any adverse effect, GI symptoms, neuropsychiatric disturbances, and less mood disturbance compared to mefloquine; Doxycycline had fewer neuropsychiatric events than mefloquine; Doxycycline and Atovaquone-proguanil had similar adverse events.

Conclusion: Atovaquone-proguanil or doxycycline as prophylaxis against malaria is best tolerated in terms of adverse effects.

Treatment and Prevention

- no treatment required for immunocompetent hosts except supportive care
- in HIV try HAART to restore immunity; if fails, try nitazoxanide
- good personal hygiene, water filtration

Plasmodium spp. (Malaria)

Microbiology

- species include: *P. falciparum* (most common and most lethal), *P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi* (new species isolated from primates in Malaysia, potentially fatal)
- complex life cycle: human host for asexual reproduction and mosquito for sexual reproduction
- sporozoites from mosquitos infect liver cells in which parasites multiply and are released as merozoites which infect RBCs causing disease
- *P. ovale* and *P. vivax* can produce dormant hypnozoites in the liver that may cause latent and/or recurrent malarial attacks

Transmission

- reservoir: infected human (see Figure 8)
- transmission by the night-biting female *Anopheles* mosquito, congenital and blood transfusion
- occurs in tropical and subtropical regions

Clinical Features

- flu-like prodrome
- paroxysms of high fever and shaking chills (due to synchronous systemic lysis of RBC) – lasts several hours
 - *P. vivax* and *P. ovale*: chills and fever q48h but can be variable
 - *P. malariae*: chills and fever q72h but can be variable
 - *P. falciparum*: less predictable fever interval, can be highly variable
- abdominal pain, diarrhea, myalgia, headache, and cough
- hepatosplenomegaly
- thrombocytopenia very common

Complications

- *P. falciparum*: CNS involvement (cerebral malaria = seizures and coma), severe anemia, acute renal failure, ARDS
- *P. falciparum* is primarily responsible for fatal disease, also *P. knowlesi*, and rarely *P. vivax*

Investigations

- microscopy, blood should be examined at 12-24 hour intervals (x3) to rule out infection
 - thick smear (Giemsa stain) indicates presence of organisms
 - thin smear (Giemsa stain) for species identification and quantification of parasites
- rapid antigen detection tests (RDT)

Treatment and Prevention

- *P. vivax*, *P. ovale*: chloroquine (and primaquine to eradicate liver forms)
- *P. vivax*, chloroquine resistant: primaquine with quinine and doxycycline or tetracycline or mefloquine
- *P. malariae*, *P. knowlesi*: chloroquine
- *P. falciparum*: most areas of world show chloroquine resistance
 - artemisinin combination therapy
 - atovaquone/proguanil combination (Malarone®)
 - quinine plus doxycycline, tetracycline or clindamycin
 - alternative is mefloquine alone but there is an increased risk of side effects
- prevented by antimalarial prophylaxis, bed nets, insect repellent, mosquito avoidance measures

Toxoplasma gondii

Transmission

- acquired through exposure to cat feces, ingestion of undercooked meat, vertical transmission, organ transplantation, whole blood transfusions

Clinical Features

- congenital
 - result of acute primary infection of mother during pregnancy
 - stillbirth, chorioretinitis, blindness, seizures, severe developmental delay, microcephaly
 - initially asymptomatic infant may develop reactivation of chorioretinitis as adolescent or adult → blurred vision, scotoma, ocular pain, photophobia, epiphora, hearing loss, developmental delay

- acquired
 - usually asymptomatic or mononucleosis-like syndrome in immunocompetent patient
 - infection remains latent for life unless reactivation due to immunosuppression
- immunocompromised (most commonly AIDS with CD4 <200)
 - encephalitis with focal CNS lesions seen as single or multiple ring-enhancing masses on CT (headache and focal neurological signs)
 - lymph node, liver and spleen enlargement and pneumonitis
 - chorioretinitis

Investigations

- serology, CSF Wright-Giemsa stain, antigen or DNA detection (PCR); pathology provides definitive diagnosis
- immunocompromised patients: consider CT scan (ring-enhancing lesion in cortex or deep nuclei) and ophthalmologic examination
- negative serology in many AIDS patients

Treatment and Prevention

- no treatment if immunocompetent, not pregnant and no severe organ damage
- in pregnancy use spiramycin to prevent transplacental transmission or pyrimethamine + sulfadiazine (add folinic acid)
- corticosteroids for eye disease, meningitis
- cook meat thoroughly
- in pregnancy, avoid undercooked meat and refrain from emptying cat litter boxes
- for prophylaxis in AIDS, see HIV section (see Table 20)

Helminths

Schistosoma spp.

Species

- *S. mansoni*, *S. hematobium*, *S. japonicum*

Transmission

- larvae (cercariae), released from snails, penetrate unbroken skin in infested fresh water (see Figure 10)
- adult worms live in terminal venules of bladder/bowel passing eggs into urine/stool
- eggs must reach fresh water to hatch; schistosomes cannot multiply in or pass between humans

Clinical Features

- pruritic skin rash at site of penetration (cercarial dermatitis)
- Katayama fever: hypersensitivity to migrating parasites (4-8 weeks after infection)
 - fever, hives, headache, weight loss, cough, abdominal pain, chronic diarrhea, eosinophilia

Complications of Chronic Infection

- caused by granulomatous response and fibrosis secondary to egg deposition by adults in the veins surrounding the intestine or bladder
- *S. mansoni*, *S. japonicum*
 - worms in mesenteric vein, eggs in portal tracts of liver and bowel
 - heavy infections: intestinal polyps, portal and pulmonary hypertension, splenomegaly (2° to portal HTN), hepatomegaly
- *S. hematobium*
 - worms in vesical plexus, eggs in distal ureter and bladder induce granulomas and fibrosis
 - hematuria and obstructive uropathy; associated with squamous cell bladder cancer
- neurologic complications: spinal cord neuroschistosomiasis (transverse myelitis), cerebral or cerebellar neuroschistosomiasis (increased ICP, focal CNS signs, seizures)
- pulmonary complications: granulomatous pulmonary endarteritis, pulmonary hypertension, cor pulmonale; especially in patients with hepatosplenic involvement

Investigations

- serology (very sensitive and specific), eosinophilia, anemia, thrombocytopenia
- *S. mansoni*, *S. japonicum*: eggs in stool, liver U/S shows fibrosis, rectal biopsy
- *S. hematobium*: bladder biopsy, eggs in urine and occasionally stool, kidney and bladder U/S

Treatment and Prevention

- praziquantel 20 mg/kg PO BID-TID x 1 day (total dose 40-60 mg/kg/day for 1 day)
- proper disposal of human fecal waste, molluscicide, avoidance of infested water



1/3 of Ontario's population is infected with *Toxoplasma gondii*.

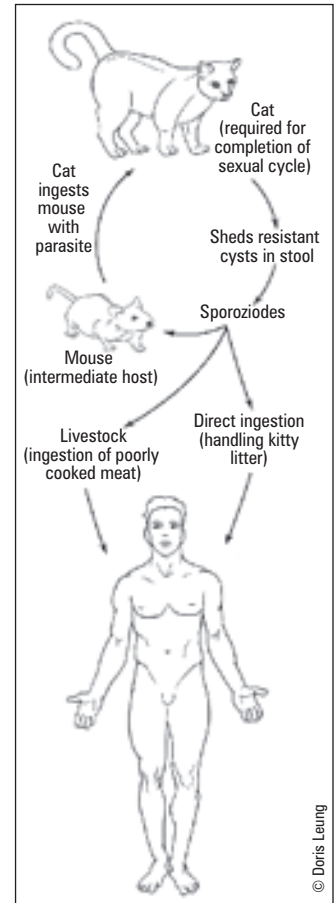


Figure 9. Life Cycle of *Toxoplasma gondii*

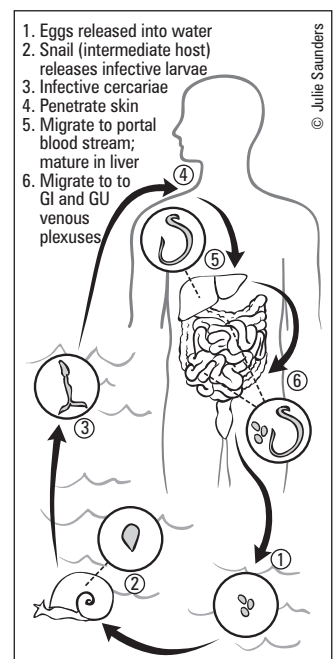


Figure 10. Life Cycle of *Schistosoma*

Cestodes/Trematodes (flatworms)

Table 23. Cestodes/Trematodes (flatworms)

Cestode	Epidemiology	Transmission	Medical Importance	Treatment
<i>Taenia solium</i>	Developing countries	Undercooked pork (larvae), human feces (eggs)	Mild abdo symptoms Cysticercosis: mass lesions in CNS, eyes, skin, seizures	Corticosteroids + Albendazole for cysticercosis Antiepileptics if seizures Praziquantel for adult tapeworm in gut
<i>Taenia saginata</i>	Developing countries	Undercooked beef (larvae)	Mild GI symptoms	Praziquantel
<i>Diphyllobothrium latum</i>	Europe, North America, Asia	Raw fish	B ₁₂ deficiency leading to macrocytic anemia and posterior column deficits	Praziquantel
<i>Echinococcus granulosus</i>	Rural areas Sheep raising countries	Dog feces (eggs)	Liver/lung cysts (enlarge between 1-20 yrs; may cause mass effect) Risk of anaphylaxis if cystic fluid released during surgical evacuation	Albendazole alone Surgery + perioperative albendazole Percutaneous aspiration + perioperative albendazole
<i>Clonorchis sinensis</i> (trematode)	Japan, Taiwan, China, SE Asia	Raw fish	Exists in bile ducts, causes inflammation and sometimes cholangiocarcinoma	Praziquantel

Nematodes (roundworms)

Table 24. Nematodes (roundworms)

Nematode	Epidemiology	Transmission	Medical Importance	Treatment
<i>Ascaris lumbricoides</i>	Tropics	Human feces	Abdo pain and intestinal obstruction from high worm burden Cough, dyspnea, pulmonary infiltrates from larval migration through lungs (Löfller's syndrome)	Mebendazole OR Albendazole OR Pyrantel pamoate
<i>Trichuris trichiura</i> (whipworm)	Tropics	Ingestion of eggs in soil	Diarrhea, abdo pain, rectal prolapse, stunted growth	Mebendazole OR Albendazole
<i>Onchocerca volvulus</i>	Africa, Latin America	Blackfly bite	River blindness (onchocerciasis)	Ivermectin, + doxycycline
<i>Wuchereria bancrofti</i>	Tropics	Mosquito bite	Damage to lymphatics resulting in lymphadenopathy and elephantiasis Tropical Pulmonary Eosinophilia	Diethylcarbamazine + doxycycline
<i>Loa Loa</i>	Central Africa	Deer Fly	Subcutaneous migration of worm	Diethylcarbamazine, removal of adult
<i>Enterobius vermicularis</i> – see ID43				
<i>Strongyloides stercoralis</i> – see ID43				

***Enterobius vermicularis* (pinworm)**

Transmission

- humans only host
- adult worms live in cecum and migrate at night to perianal skin to deposit eggs
- fecal-oral self-inoculation and person to person spread, fomite transmission

Clinical Features

- asymptomatic carrier state
- severe nocturnal perianal itching (pruritus ani)
- occasionally vaginitis
- abdominal pain, nausea, vomiting

Investigations

- sticky tape test (5-7 tests to rule out infection): eggs adhere to tape applied to perianal skin
- examination of perianal area at night may reveal adult worms seen with unaided eye
- usually no eosinophilia since no tissue invasion

Treatment and Prevention

- mebendazole, albendazole, pyrantel pamoate
- clean underwear change, pajamas to sleep, bathe in morning, wash hands after bowel movement, trim fingernails
- treat all members of family simultaneously
- reinfection common

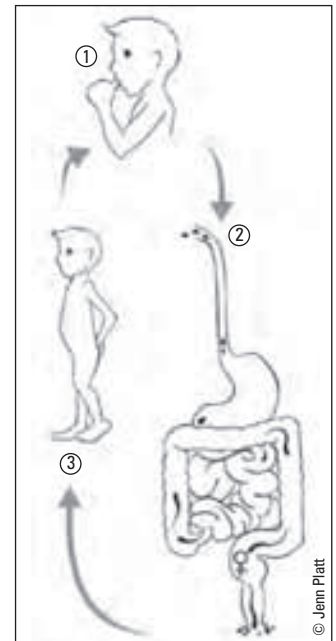


Figure 11. Life Cycle of *Enterobius*

***Strongyloides stercoralis* (threadworm)**

Transmission

- through unbroken skin, barefoot walking in tropics/subtropics
- adult worms live embedded in mucosa of small intestine
- one of the only worms capable of multiplying in human host
- source of infection: fecal contamination of soil

Clinical Features

- mostly asymptomatic
- pruritic dermatitis at site of larval penetration
- transient pulmonary symptoms during pulmonary migration of larvae (eosinophilic pneumonitis = Löfller's syndrome – see [Respirology](#), R12)
- abdominal pain, diarrhea
- hyperinfection: occasional fatal cases caused by massive auto-infection in immunocompromised host (pneumonia, ARDS, multi-organ failure, enteritis, Gram-negative bacteremia); immunoablative therapy is the most common risk factor for disseminated infection

Investigations

- fecal exam for larvae (no eggs) 3-4 weeks after infection, larval culture on agar
- small bowel biopsy
- serology (most sensitive), eosinophilia (in chronic but not hyperinfection phase)

Treatment

- ivermectin, 200 mcg/kg/d PO x 2 days (albendazole 400 mg PO bid x 7 days, less effective)

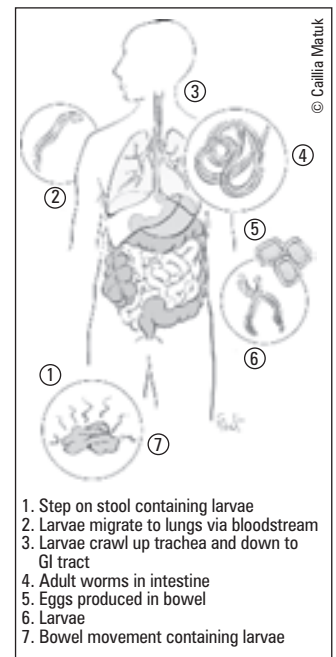


Figure 12. Life Cycle of *Strongyloides*

Infections in the Immunocompromised Host

- immunocompromised hosts have increased susceptibility to infections from pathogens that are typically low virulence, commensal, or latent
- type of immunosuppression predicts probable spectrum of agents

Factors that Compromise the Immune System

- general: age (very young or elderly), malnutrition
- immune disease: HIV/AIDS, malignancies, asplenia, hypogammaglobulinemia, neutropenia
- other disease: DM, malignancy
- iatrogenic: corticosteroids, chemotherapy, radiation treatment, anti-TNF therapy, other immunosuppressive drugs (e.g. in transplant patients)

**Infections associated with Asplenia**

Hemophilus influenza B
Streptococcus pneumoniae
Neisseria meningitidis
Salmonella
Babesiosis
Malaria
Capnocytophaga canimorsus

Table 25. Types of Immunocompromise

Type	Conditions	Vulnerable To
Cell-Mediated Immunity	HIV, Hodgkin's, hairy cell leukemia, cytotoxic drugs, SCID, DiGeorge syndrome	Latent viruses Fungi Parasites
Humoral Immunity	CLL, lymphosarcoma, multiple myeloma, nephrotic syndrome, protein-losing enteropathy, burns, sickle cell anemia, asplenia, splenectomy, selective Ig deficiencies, Wiskott-Aldrich syndrome	Encapsulated organisms (<i>S. pneumo</i> , <i>H. flu</i> , <i>N. meningitidis</i> , <i>Salmonella typhi</i> , Group B strep)
Neutrophil Function	Myelodysplasia, paroxysmal nocturnal hemoglobinuria, radiation, cytotoxic drug therapy, C3 or C5 deficiencies, chronic granulomatous disease	Catalase-producing organisms (<i>Staphylococcus</i> , <i>Serratia</i> , <i>Nocardia</i> , <i>Aspergillus</i>)

**Febrile Neutropenia**

- fever ($\geq 38.3^{\circ}\text{C}$ or $\geq 38.0^{\circ}\text{C}$ for ≥ 1 hour) and ANC < 0.5 or < 1.0 but trending down to 0.5

Pathophysiology

- decreased neutrophil production
 - marrow: infection, aplastic/myelophthisic anemia, leukemia, lymphoma, myelodysplastic syndromes
 - iatrogenic: cancer chemotherapy, radiation, drugs
 - deficiencies: vitamin B₁₂, folate
- increased peripheral neutrophil destruction
 - autoimmune: Felty's syndrome, SLE, antineutrophil antibodies
 - splenic sequestration, peripheral margination, hemodialysis, cardiopulmonary bypass

Etiology

- GN (especially *Pseudomonas*) historically most common
- GP more common now
- fungal superinfection if neutropenia prolonged or if concurrent antibiotic use (especially *Candida*, *Aspergillus*)

Investigations

- examine for potential sites of infection: mucositis and line infections are most common
- do NOT perform DRE; examine perianal region
- CXR, blood culture, urine culture, culture all indwelling catheter ports

Treatment

- most hospitals have their own specific protocol; one example is presented below



ANC (absolute neutrophil count) =
 $\text{WBC} \times (\% \text{neutrophils} + \% \text{bands})$



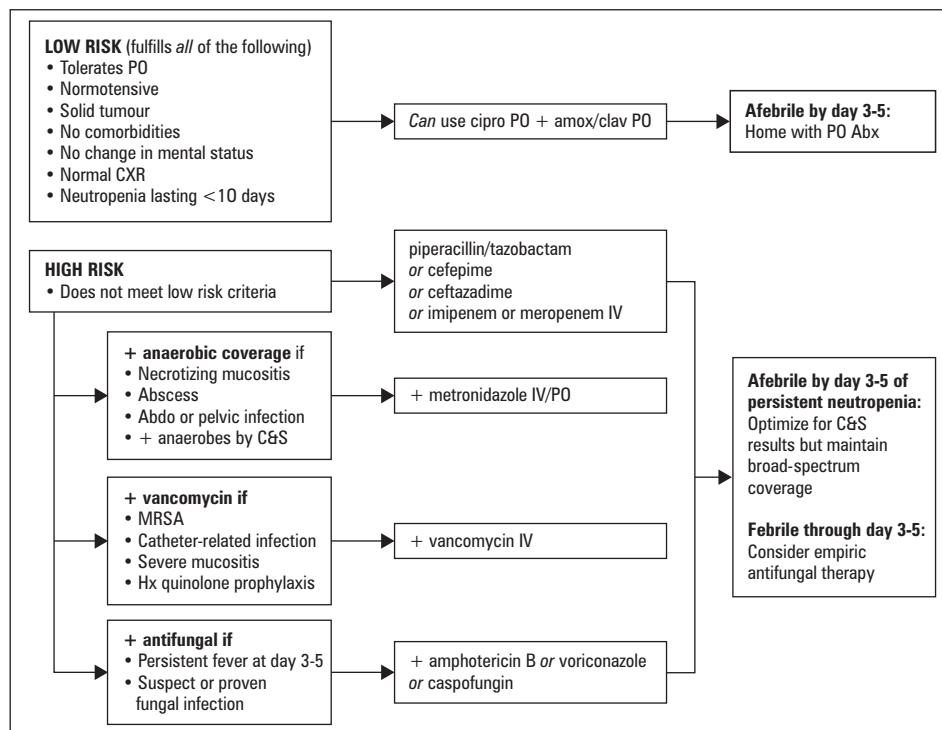
Usual signs and symptoms of infection may be diminished because neutrophils are required for a robust inflammatory response. Exam and X-ray findings may be more subtle.



WBC is lowest between 5-10 days after last chemo cycle.



Prophylaxis against FN with G-CSF and GM-CSF decreases hospitalization without affecting mortality (indicated if risk of FN 20% or if FN has occurred in a previous chemo cycle).

**Figure 13. Example of Treatment Protocol for Febrile Neutropenia**

Infections in Solid Organ Transplant Recipients

- infection is a leading cause of early morbidity/mortality in these transplant recipients
- infection depends on degree of immunosuppression
- common infections <1 month post-transplant: bacterial infection of wound/lines/lungs herpetic stomatitis
- common infections >1 mo post-transplant
 - viral (especially CMV, EBV, VZV)
 - fungal (especially *Aspergillus*, *Cryptococcus*, *P. jiroveci*)
 - protozoan (especially *Toxoplasma*)
 - unusual bacterial/mycobacterial infections (especially TB, *Nocardia*, *Listeria*)

Prophylactic Vaccinations Given Before Transplant

- to all transplant patients: Td, Pneumovax®, hepatitis A and B vaccines
- if low titre or poor documentation: MMR, polio, varicella vaccination (with booster 4-8 weeks later)

Immune Reconstitution Syndrome

- a harmful inflammatory response directed against a previously acquired infection following a recovery of the immune system

Etiology

- paradoxical worsening of a successfully or partially treated opportunistic infection
- new onset response to a previously unidentified opportunistic infection
- the majority of cases are in HIV/AIDS or immunosuppressed patients starting anti-retroviral therapy or discontinuing immunosuppressive therapy; sudden recovery of CD4 T-cells results in fever and inflammation directed towards subclinical infection
- can occur in response to multiple infections:
 - *Mycobacteria* (tuberculosis, avium complex)
 - *Cryptococcus*
 - *Pneumocystis*
 - *Toxoplasma*
 - Hepatitis B and C
 - Herpes viruses (zoster, simplex, cytomegalovirus)
 - JC virus (progressive multifocal leukoencephalopathy)
 - *Molluscum contagiosum*
- must recognize clinical features of specific infection
- thought to be worse with quick increase in CD4 count and with lower CD4 count
- non-HIV conditions with documented immune reconstitution syndrome: solid organ transplant recipients, post-partum women, neutropenic patients, anti-TNF therapy

Epidemiology

- in HIV patients starting HAART, immune reconstitution syndrome reported to affect ~10%

Treatment

- continue HAART therapy in HIV patients with mild-moderate symptoms, but consider discontinuation if symptoms are life-threatening or potentially irreversible
- treat underlying infection; initiate treatment for some infections prior to HAART initiation
- consider starting corticosteroids



Fever of Unknown Origin (FUO)

Table 26. Classification of Fever of Unknown Origin (FUO) – Temp >38.3°C on several occasions

Classical FUO	Nosocomial FUO	Neutropenic FUO	HIV-associated FUO
Duration >3 weeks	(infection not present/ incubating on admission)	Neutrophil count <500/mL or is expected to fall to that level in 1-2 days	HIV infections
Diagnosis uncertain after 3 outpatient visits or 3 days in hospital or 1 week of “intelligent and invasive” ambulatory investigation	Diagnosis uncertain after 3 days of investigation, including at least 2 days incubation of cultures	Diagnosis uncertain after 3 days of investigation, including at least 2 days incubation of cultures	Duration >4 weeks for outpatients, >3 days for hospitalized patients Diagnosis uncertain after 3 days of investigation, including at least 2 days incubation of cultures



Fever Post-International Travel Key elements in history include:

- Travel location
- Exposures, risk factors
- Fever onset and duration
- Immunization status
- Antimalarial prophylaxis and adherence
- Presence of diarrhea and/or skin manifestations



Causes of Nosocomial FUO

B, C, D, E

Bacterial and fungal infections of
respiratory tract and surgical sites
Catheters (intravascular and urinary)

Drugs
Emboli

Etiology Classic FUO

- infectious causes (15-25%)
 - TB – usually extra-pulmonary, miliary or pulmonary in patients with pre-existing pulmonary disease
 - abscess – usually in abdomen or pelvis; risk factors include cirrhosis, steroids or other immunosuppressive medications, recent surgery, diabetes
 - osteomyelitis
 - bacterial endocarditis – cultures negative in 2-5%
 - uncommonly toxoplasmosis, Leishmania, amoebiasis, histoplasmosis, Cryptococcus
- neoplastic causes (<20%)
 - most commonly lymphomas (especially non-Hodgkin's) and leukemias
 - solid tumours: RCC most common, also breast, liver, colon, pancreas or liver metastases
 - malignant histiocytosis: rare but rapidly progressive with high fever, weight loss, lymphadenopathy, hepatosplenomegaly
- collagen vascular diseases (15-25% of cases)
 - SLE, RA, rheumatic fever, vasculitis, especially temporal arteritis, JRA, Still's disease
- miscellaneous (15-20% of cases)
 - drug fever: commonly antibiotics, antiarrhythmics, methyldopa, phenytoin, NSAIDs
 - sarcoidosis
 - Familial Mediterranean Fever
 - venous thromboembolic disease
- unknown despite investigations

Approach to Classic FUO

- history: travel, environmental/occupational exposures, infectious contacts medication history, immunizations, TB history, sexual history, past medical history
- thorough review of systems including symptoms that resolved before interview
- daily physical exam to assess fever pattern, look for rashes, murmurs, arthritic signs, lymphadenopathy
- initial investigations
 - bloodwork: CBC with differential and film, electrolytes, BUN, Cr, calcium profile, LFTs, ESR, CRP, muscle enzymes, RF, ANA, serum protein electrophoresis
 - cultures: blood (x 2 sets), urine, sputum, stool C&S, O&P, other fluids as appropriate
 - heterophile Ab (mononucleosis), CMV antigenemia test, HIV serology
 - CXR
- if there are diagnostic clues from any of the above steps, proceed with directed exam, biopsies or invasive testing as required followed by directed treatment once a diagnosis is established
- if no diagnosis with the above, consider empiric therapy vs. watchful waiting
 - prognosis for most patients with FUO persisting without a diagnosis is very good without intervention

Nosocomial Infections

- nosocomial infections are infections acquired >48 hrs after admission to a healthcare facility or within 30 days from discharge
- risk factors include prolonged hospital stay, antibiotic use, surgery, hemodialysis, intensive care, colonization with a resistant organism, immunodeficiency
- these patients have higher mortality, longer hospital stays, and higher health-care costs
- hand hygiene is an essential precaution

Table 27. Common Nosocomial Infectious Agents

Bacteria	Characteristics	Manifestation	Investigations	Management
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Gram-positive cocci	Skin and soft tissue infection Bacteremia Pneumonia	Admission screening culture from nares and peri-anal region identifies colonization Culture of infection site CXR	Contact precautions Vancomycin or linezolid for infection 2% chlorhexidine wash OD x7d + rifampin 300mg PO BID x7d + doxycycline 100mg PO x 7d + mucopirocin cream BID to nares x7d to decolonize
Vancomycin-resistant <i>Enterococcus</i>	Majority are <i>E. faecium</i> Resistant if minimum inhibitory concentration of vancomycin is ≥ 32 $\mu\text{g/mL}$	Rarely causes disease in healthy people UTI Bacteremia Endocarditis	Rectal or perirectal swab OR stool culture for colonization Culture of infected site	Contact precautions Ampicillin if susceptible Otherwise, linezolid, tigecycline, or daptomycin depending on site of infection No effective decolonization methods identified
<i>Clostridium difficile</i>	Releases exotoxins	Fever, nausea, anorexia Watery diarrhea \pm occult blood Severe: toxic megacolon Risk bowel perforation Associated with antibiotic leukocytosis	Stool toxin assays endoscopy (if not suspect fulminant colitis) AXR (may see colonic dilatation)	Contact precautions Stop culprit antibiotic therapy Supportive therapy (IV fluids) Mild-moderate disease: metronidazole 500 mg PO TID Severe disease: vancomycin 125 mg PO QID
Extended spectrum beta-lactamases (e.g. <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i>)	Resistant to most beta-lactam producing antibiotics e.g. penicillins, aztreonam and cephalosporins	UTI Pulmonary infection Bacteremia Liver abscess in susceptible patients Meningitis	Blood, sputum, urine, or aspirated body fluid culture Imaging at infection site (CXR, CT, U/S)	Droplet or contact precautions Dependent on culture and sensitivity results, carbapenems can be used for empiric therapy

Travel Medicine

General Travel Precautions

- vector-borne: long-sleeves, long pants, hats, repellents (permethrin containing) applied to clothes, belongings and bed nets, repellents (DEET) to skin
- food/water: avoid eating raw meats/seafood, uncooked vegetables and milk/dairy products; drink only carbonated beverages, chlorinated water, boiled water, beer, wine
- recreation: caution when swimming in schistosomiasis-endemic regions, beaches that may contain human/animal waste products, near storm drains, after heavy rainfalls
- prophylaxis: malaria (chloroquine, mefloquine, atovaquone + proguanil, doxycycline), traveler's diarrhea (Pepto-Bismol, fluoroquinolones)
- vaccines: hepatitis A/B, Japanese encephalitis, typhoid fever, yellow fever, rabies, ETEC
- all travellers should have standard vaccines up to date (HepB, MMR, tetanus/diphtheria, varicella, pertussis, polio)
- sexually transmitted infections: safer sex practices

Infectious Diseases to Consider

- vector borne: malaria, dengue fever, yellow fever, Rickettsia, West Nile virus, trypanosomiasis, Japanese encephalitis, tick-borne encephalitis, spotted fever, leishmaniasis
- sexually transmitted: HIV, HepB, syphilis, usual STDs
- zoonotic: rabies, hantavirus, tularemia, Q fever, anthrax, brucellosis
- airborne: TB
- food/water: HepA/E, brucellosis, typhoid, paratyphoid, amebiasis, dysentery, traveller's diarrhea, cholera, *Campylobacter*
- soil/water: schistosomiasis, strongyloidiasis, leptospirosis, cutaneous larva migrans, histoplasmosis, paracoccidioidomycosis



For up to date information on geographic and seasonal patterns of disease and travel advisories, check the website for the United States Centers for Disease Control and Prevention (www.cdc.gov/travel) or Foreign Affairs Canada (voyage.gc.ca).

Fever in the Returned Traveller

Detailed History

- pre-travel preparation
 - immunizations
 - malaria prophylaxis
 - other
- travel itinerary
 - countries/areas visited
 - exact arrival and departure dates (to determine incubation period)
 - dates of travel (season)
- exposure history
 - uncooked meat/dairy
 - fresh water exposure
 - injections (tattoos, drugs)
 - animal/insect bites
 - sexual
- fever pattern
 - see Table 28

Table 28. Fever in the Returned Traveller

Illness	Geography	Pathogen	Incubation Period	Clinical Manifestations	Diagnosis	Treatment
Malaria	Africa India C. and S. America SE Asia	<i>Plasmodium falciparum</i> <i>Plasmodium vivax</i> <i>P. malariae</i> <i>P. ovale</i> <i>P. knowlesi</i>	10 days to 40 years	Fever and flu-like illness, (shaking chills, headache, muscle aches, and fatigue) Nausea, vomiting, and diarrhea Anemia and jaundice <i>Plasmodium falciparum</i> : (severe) kidney failure, seizures, mental confusion, prostration, coma, death, respiratory failure	Blood smear (thick and thin) x3 Antigen detection PCR (mostly a research tool)	Artesunate (for severe disease) + malarone, doxycycline, or clindamycin Quinine sulfate + doxycycline or clindamycin Chloroquine + primaquine
Dengue	South East Asia Caribbean	Dengue viruses (4)	3 days to 2 weeks	Sudden onset of fever Headache Retro-orbital pain Myalgias and arthralgias Leukopenia Thrombocytopenia Hemorrhagic manifestations (rare in travelers)	Anti-dengue IgM positivity	Symptom relief: Acetaminophen (avoid using NSAIDs because of anticoagulant properties)
Typhoid (enteric fever)	Global but mostly Indian subcontinent	<i>Salmonella Typhi</i> <i>Salmonella Paratyphi</i>	3 to 60 days	Sustained fever 103° to 104° F (39° to 40° C) Stomach pains, headache, loss of appetite Cough Constipation	Stool, urine or blood sample positive for <i>S. Typhi</i> or <i>S. Paratyphi</i>	Quinolone antibiotic (e.g. ciprofloxacin), ceftriaxone or macrolide
Tick typhus	Mediterranean South Africa India	<i>Rickettsia</i>	1 to 2 weeks	Fever Headache Fatigue Muscle aches Occasionally rash Eschar at site of tick bite Thrombocytopenia Elevated liver enzymes	Serology Presence of classic tick eschar	Doxycycline
TB	Global	<i>M. tuberculosis</i>	Variable	Fever Cough Hemoptysis	Tuberculin skin test CXR Sputum culture and AFB	Ethambutol, isoniazid, pyrazinamide, rifampin

Antimicrobials

Antibiotics

- assume no anaerobic coverage unless specifically mentioned
- assume not MRSA or VRE unless specified



Reasons for Combination Therapy

- Polymicrobial infection
- Empiric therapy pending culture results
- Synergy for difficult to treat pathogens
- To prevent emergence of resistance

Table 29. Antibiotics

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
CELL WALL INHIBITORS					
Penicillins					
Benzyl penicillin - penicillin G IV/IM - penicillin V PO	GP <u>except</u> <i>Staphylococcus</i> , <i>Enterococcus</i> Oral anaerobes <u>except</u> <i>Bacteroides</i> , <i>Treponema</i>	Bactericidal: β -lactam inhibits penicillin binding protein (PBP) and prevents cross- linking of peptidoglycans	Immediate allergy (IgE): anaphylaxis, urticaria Late-onset allergy (IgG): urticaria, rash, serum sickness Interstitial nephritis Dose related toxicity: seizures, electrolyte disturbance, bleeding diathesis Diarrhea	Mild to moderately severe infections caused by susceptible organisms including actinomycosis, streptococcal pharyngitis, streptococcal skin and soft tissue infections, syphilis	Hypersensitivity to penicillin
Aminopenicillin - ampicillin IV - amoxicillin PO (Amoxil®)	Same as penicillin <i>Enterococcus</i>			Bacterial meningitis and endocarditis (ampicillin), AOM, streptococcal pharyngitis, sinusitis, acute exacerbations of COPD, part of <i>H. pylori</i> treatment, Lyme disease, RTI, UTI (amoxicillin and ampicillin)	Hypersensitivity to penicillin or β -lactam antibiotics
Isoxazolyl penicillin - cloxacillin - methicillin - nafcillin - oxacillin	Same as penicillin <i>Staphylococcus</i>			Bacterial infections from susceptible penicillinase- producing staphylococci, skin soft-tissue infections	Hypersensitivity to cloxacillin or any penicillin
Ureidopenicillin - piperacillin	Same as penicillin GNB including <i>Pseudomonas</i> Anaerobes <i>Enterococcus</i>			Pip-tazo (Tazocin®) used for systemic and/or local bacterial infections, caused by piperacillin resistant, piperacillin/tazobactam susceptible, β -lactamase producing strains including certain abdominal, skin, and gynecological infections and pneumonias	History of allergic reactions to any penicillin, cephalosporin or β -lactamase inhibitor
Lactamase Inhibitors - amoxicillin clavulanate (Clavulin®, Augmentin®) - tazobactam	Same as penicillin <i>Staphylococcus</i> <i>H. influenzae</i> <i>Enterococcus</i>			Various β -lactamase producing bacteria, Clavulin® sensitive bacteria including RTI, sinusitis, AOM, skin and soft tissue infections, UTI Same as for ureidopenicillin	Hypersensitivity to penicillin or cephalosporin History of Clavulin®-associated jaundice or hepatic dysfunction
Carboxypenicillin - carbenicillin	Same as penicillin Extended GN coverage				

RTI = respiratory tract infection

Table 29. Antibiotics (continued)

Class and Drugs		Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications	
CELL WALL INHIBITORS							
Cephalosporins							
PO 1° cephalexin (Keflex®)	IV cefazolin (Ancef®)	GP <u>except</u> <i>Enterococcus</i>	GN <u>Only</u> <i>E. coli</i> , <i>Klebsiella</i> , <i>Proteus</i>	β-lactam inhibits PBP and prevents cross-linking of peptidoglycans	10% penicillin allergy cross-reactivity Nephrotoxicity	Skin and soft tissue infections, prevention of surgical site infections (cefazolin); infections caused by susceptible organisms	Hypersensitivity to cephalosporins or other β-lactam antibiotic
2° cefuroxime (Ceftin®)	cefuroxime (Zinacef®)	Weaker activity than 1°	More coverage than 1° (^A includes anaerobes)			Soft tissue	Hypersensitivity to cephalosporins or other β-lactam antibiotic
cefprozil (Ceftzil®)	cefotaxime (Claforan®)						
3° cefixime (Suprax®)	ceftriaxone (Rocephin®) ceftazidime ^B (Fortaz®)	<i>S. aureus</i> + good streptococcal coverage (^B not reliable against GP)	Broad coverage (^B includes <i>Pseudomonas</i>)			RTI, gonorrhea (use cefixime), meningitis, septicemia, abdominal infections	Hypersensitivity to cephalosporins or other β-lactam antibiotic
4°	cefepime (Maxipime®)	Broad spectrum	Broad coverage including <i>Pseudomonas</i>			Empiric therapy for febrile neutropenia	Hypersensitivity to cephalosporins or other β-lactam antibiotic
Carbapenems							
imipenem (Primaxin®)		GP <u>except</u> <i>Enterococcus</i> , MRSA GN including <i>Pseudomonas</i> + <i>Enterobacter</i> Anaerobes	β-lactam inhibits PBP and prevents cross-linking of peptidoglycans	Penicillin allergy cross-reactivity Seizures	Treatment of infections caused by GNB producing extended-spectrum β-lactamases, serious infections caused by susceptible organisms	Hypersensitivity to imipenem	
meropenem (Merrem®)							
Vancomycin (Vancocin®)		GP including MRSA, not VRE <i>C. difficile</i> if PO	Glycopeptide sterically inhibits addition of peptidoglycan subunits	Red Man Syndrome (histamine rxn with decreased BP) Nephrotoxicity Ototoxicity Neutropenia Thrombocytopenia	Severe or life-threatening GP infections, patients with β-lactam allergy May be taken only orally for pseudomembranous colitis	Hypersensitivity to vancomycin	
Teicoplanin		GP including MRSA, not most VRE	Glycopeptide sterically inhibits addition of peptidoglycan subunits				
PROTEIN SYNTHESIS INHIBITORS (50S RIBOSOME)							
Macrolides							
erythromycin (Erybid®, Eryc®)		GP <u>except</u> <i>Enterococcus</i> GN: <i>Legionella</i> , <i>B. pertussis</i> “Atypicals”: <i>Chlamydia</i> , <i>Mycoplasma</i>	Inhibits 50S ribosome	GI upset Acute cholestatic hepatitis Prolonged QT	Susceptible RTI, pertussis, diphtheria, Legionnaires’ Disease, skin and soft tissue infections	Hypersensitivity to erythromycin Concurrent therapy with astemizole, terfenadine	
clarithromycin (Biaxin®)					Susceptible RTI, skin infections, mycobacterial infections, part of <i>H. pylori</i> treatment	Hypersensitivity to macrolides Concurrent therapy with astemizole, terfenadine, or pimoizide	
azithromycin (Zithromax®)					Susceptible pharyngitis, tonsillitis, AOM, acute exacerbations of COPD, community-acquired pneumonia, skin infections, campylobacter infections if treatment indicated, chlamydia	Hypersensitivity to macrolides	

Table 29. Antibiotics (continued)

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
PROTEIN SYNTHESIS INHIBITORS (50S RIBOSOME)					
Lincosamides					
clindamycin (Dalacin®)	GP <u>except</u> <i>Enterococcus</i> , some MRSA Anaerobes	Inhibits peptide bond formation at 50S ribosome	Pseudomembranous colitis GI upset	Treatment of suspected or proven infections caused by GP, anaerobes	Hypersensitivity to clindamycin or lincomycin Infants <30 days
chloramphenicol	GP GN Anaerobes	Inhibits peptidyl transferase action on tRNA at 50S ribosome	Aplastic anemia Grey baby syndrome	Serious infections by susceptible organisms when suitable alternatives are not available	Hypersensitivity to chloramphenicol
linezolid (Zyvoxam®)	GP including VRE + MRSA	Binds 50S to prevent functional 70S initiation complex	HTN (acts as MAOI) Risks with prolonged use: myelosuppression optic neuropathy, peripheral neuropathy	Vancomycin-resistant <i>Enterococcus faecium</i> infections including intra-abdominal, skin and skin-structure, and urinary tract infections, MRSA infections as out patient therapy	Hypersensitivity to linezolid
PROTEIN SYNTHESIS INHIBITORS (30S RIBOSOME)					
Aminoglycosides					
gentamicin tobramycin ^c neomycin streptomycin amikacin (Amikin®)	GN (^c <u>includes</u> <i>Pseudomonas</i>)	Binds 30S, causing mRNA to be misread	Nephrotoxicity Ototoxicity	Gram-negative infections when alternatives do not exist UTIs, used in low doses for synergy with beta-lactams or with vancomycin in infective endocarditis	Hypersensitivity or previous ototoxic reaction to aminoglycosides
Tetracyclines					
tetracycline (Apo-Tetra®, Nu-TetraT®) minocycline (MinocinT®) doxycycline ^d (Doxycin®)	GP Anaerobes Atypicals: <i>Chlamydophila</i> , <i>Mycoplasma</i> , <i>Rickettsia</i> , <i>Borrelia burgdorferi</i> ^d Malaria prophylaxis	Blocks A site of 30S ribosome	GI upset Hepatotoxicity Fanconi's syndrome Photosensitivity Teratogenic Yellow teeth and stunted bone growth in children	Rickettsial infections, <i>Chlamydophila</i> , acne (tetracycline), PID (step-down), malaria prophylaxis (doxycycline)	Hypersensitivity to any tetracycline Severe renal or hepatic dysfunction Pregnancy or lactation Children under 8 years
TOPOISOMERASE INHIBITORS					
Fluoroquinolones					
ciprofloxacin ^E (Cipro®) norfloxacin (Apo-Norflo®) ofloxacin (Floxin®) Respiratory FQs: levofloxacin (Levaquin®) moxifloxacin ^F (Avelox®)	Poor GP activity GN (^E <u>includes</u> <i>Pseudomonas</i>) Same as above More GP coverage than ciprofloxacin Atypicals ^F Includes anaerobes No <i>Pseudomonas</i> coverage	Inhibits DNA gyrase Dysglycemia	H/A, dizziness Allergy Seizures Prolonged QT Teratogenic	Only use when necessary to prevent resistance; RTI, sinusitis (not ciprofloxacin unless susceptible organism isolated), prostatitis, bone and joint infections, skin and soft tissue infections, infectious diarrhea, meningococcal prophylaxis, intra-abdominal infections, febrile neutropenia (ciprofloxacin, levofloxacin), uncomplicated UTI (norfloxacin), pneumonia (respiratory quinolones)	Hypersensitivity to quinolones
Rifampin	GPC <i>N. meningitidis</i> <i>H. influenza</i> <i>Mycobacteria</i>	Inhibits RNA polymerase	Hepatic dysfunction, P450 Orange tears/saliva/urine	Part of treatment for active TB, alone for treatment of latent TB, part of treatment of other mycobacterial infections, endocarditis involving prosthetic valve, prophylaxis for those exposed to people with <i>N. meningitidis</i> or Hib meningitis	Jaundice Hypersensitivity to rifamycins
Metronidazole (Flagyl®)	Anaerobes Protozoa	Forms toxic metabolites in bacterial cell which damage microbial DNA	Disulfiram-type rxn with EtOH Seizures Peripheral neuropathy	Protozoal infections (<i>trichomonas</i> , <i>amebiasis</i> , <i>giardiasis</i>), bacterial vaginosis, anaerobic bacterial infections	Hypersensitivity to metronidazole

Table 29. Antibiotics (continued)

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
ANTI-METABOLITE					
Trimethoprim-Sulfamethoxazole (TMP/SMX) (Septra®, Bactrim®)	GP GN: enteric <i>Nocardia</i> Other: <i>Pneumocystis</i> , <i>Toxoplasmosis</i>	Inhibits folic acid production (TMP inhibits DHFR and SMX is a competitive inhibitor of PABA)	Hepatitis Stevens Johnson syndrome TMP: - Megaloblastic anemia - Leuko/granulocytopenia - Hyperkalemia SMX: - Hypersensitivity - Interstitial nephritis - BM suppression	Susceptible UTI, RTI, GI infections, skin and soft tissue infections, treatment and prophylaxis of <i>P. jiroveci</i> pneumonia	Hypersensitivity to TMP-SMX Porphyria
nitrofurantoin (MacroBID®, Macrochantin®)	<i>Enterococcus</i> , <i>S. saprophyticus</i> GN (coliforms)	Breaks bacterial DNA strands	Cholestasis, hepatitis Hemolysis if G6PD def Interstitial lung disease with chronic use	Lower UTI; not pyelonephritis or bacteremia	Hypersensitivity to nitrofurantoin Anuria, oliguria or significant renal impairment Pregnant patients during labour and delivery or when labour imminent Infants <1 month of age
ANTI-MYCOBACTERIALS					
isoniazid (INH)	<i>Mycobacteria</i>	Inhibits mycolic acid synthesis	Hepatitis Drug-induced SLE Peripheral neuropathy	Part of treatment for active TB, alone for treatment of latent TB	Hypersensitivity to isoniazid Drug-induced hepatitis or acute liver disease
rifampin (RIF)	GPC <i>N. meningitidis</i> <i>H. influenzae</i> <i>Mycobacteria</i>	Inhibits RNA polymerase	Hepatic dysfunction, decreased P450 Orange tears, saliva, urine	Part of treatment for active TB, alone for treatment of latent TB, part of treatment of other mycobacterial infections, endocarditis involving prosthetic valve, prophylaxis for those exposed to people with <i>N. meningitidis</i> or HiB meningitis	Jaundice Hypersensitivity to rifamycins
ethambutol	<i>Mycobacteria</i>	Inhibits mycolic acid synthesis	Loss of central and colour vision	Part of treatment for active TB and other mycobacterial infections	Hypersensitivity to ethambutol Optic neuritis unless benefits outweigh risk Renal failure
pyrazinamide (PZA)	<i>Mycobacteria</i>	Unknown	Hepatotoxicity Gout Gastric irritation	Part of treatment for active TB	Hypersensitivity to pyrazinamide Severe hepatic damage or acute liver disease Patients with acute gout
SULFONES dapson sulfoxone	<i>M. Leprae</i> , part of treatment for <i>P. jiroveci</i> pneumonia (with TMP), <i>P. jiroveci</i> pneumonia prophylaxis, Toxoplasmosis prophylaxis with pyrimethamine	Competitive inhibitor of PABA	Rash Drug fever Agranulocytosis		



Bactericidal antibiotics
Penicillins
Cephalosporins
Carbapenems
Vancomycin
Aminoglycosides
Fluoroquinolones
Metronidazole

Bacteriostatic antibiotics
Macrolides
Tetracyclines
Clindamycin/
Chloramphenicol
TMP-SMX
Linezolid
Mnemonic:
"Mack Trucks
Clog The Lanes"

Table 30. Antibiotics for Difficult Bacteria

<i>Pseudomonas</i>	<i>S. aureus</i>	<i>Enterococcus</i>	<i>H. Flu</i>	Anaerobes
ciprofloxacin	cloxacillin (MSSA)	ampicillin	amoxicillin-clavulanate	metronidazole
tobramycin	1° cephalosporin (MSSA)	amoxicillin	2°/3° cephalosporin	clindamycin
piperacillin/tazobactam	clindamycin	vancomycin	macrolides	amoxicillin-clavulanate
ceftazidime	vancomycin	nitrofurantoin (UTI)	levofloxacin	cefoxitin
cefipime			moxifloxacin	piperacillin-tazobactam
meropenem				
imipenem				

Antivirals

Table 31. Antivirals

Class and Drugs	Coverage	Mechanism of Action	Adverse effects	Contraindications
ANTI-HERPESVIRUS				
acyclovir valacyclovir (Valtrex [®]) (prodrug of acyclovir)	HSV-1,2 VZV	Guanosine analog inhibits viral DNA polymerase	PO well-tolerated IV: nephrotoxicity, CNS	Hypersensitivity to acyclovir or valacyclovir
famciclovir (Famvir [®]) penciclovir	HSV-1,2 VZV		H/A, nausea	Hypersensitivity to famciclovir or penciclovir
ganciclovir (Cytovene [®]) valganciclovir (prodrug of ganciclovir)	CMV HSV-1,2, VZV		Heme: neutropenia, thrombocytopenia, anemia GI: N/V, diarrhea	Hypersensitivity to ganciclovir or valganciclovir Possible cross- hypersensitivity between acyclovir and valacyclovir
foscarnet	CMV Acyclovir-resistant HSV, VZV	Pyrophosphate analog inhibits viral DNA polymerase	Nephrotoxicity (reversible) Anemia, electrolyte disturbances	
OTHER ANTIVIRALS				
interferon-PEG- interferon- α 2a, 2b	Chronic hep B, hep C Condyloma acuminata	Inhibits viral protein synthesis	"Flu-like" syndrome Depression Bone marrow suppression	Hypersensitivity to any interferon Cannot use in combination with ribavirin if renal impairment
ribavirin (Virazole [®])	Chronic hep C RSV Lassa fever	Guanosine analog with multiple postulated mechanisms of action	Hemolytic anemia Rash, conjunctivitis Highly teratogenic	Pregnancy or women who may become pregnant
lamivudine (3TC [®] , Heptovir [®])	Chronic hep B HIV	See HIV/AIDS section		Hypersensitivity to lamivudine
M2 inhibitors: amantadine (Endantadine [®] , Symmetrel [®]) rimantadine	Influenza A: treatment and prophylaxis	Inhibits viral uncoating after infection of cell	Anti-cholinergic effects CNS: anxiety, insomnia, H/A, dizziness, difficulty concentrating	Hypersensitivity to the drug
Neuraminidase inhibitors: zanamavir (Relenza [®]) oseltamavir (Tamiflu [®])	Influenza A and B: treatment and prophylaxis	Inhibits neuraminidase, an enzyme required for release of virus from infected cells and prevention of viral aggregation	GI: N/V, diarrhea Bronchospasm in zanamavir (rare)	Hypersensitivity to the drug



Red Man Syndrome can be reduced with a slow vancomycin infusion rate.



Prevent INH-induced peripheral neuropathy with vitamin B6 (pyridoxine).



Clindamycin has good tissue penetration, even into bone.



Chloramphenicol easily penetrates BBB.



Rifampin

- Good adjunct for treating prosthetic device infection (bacterial biofilm)
- Always used in combination with other antibiotics to reduce emergence of resistance



TMP/SMX-induced granulocytopenia may be alleviated with folic acid supplementation.

Antifungals

Table 32. Antifungals

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
POLYENES				
amphotericin B	Systemic mycoses: Histoplasmosis, Blastomycosis, Coccidiomycosis Pulmonary: Aspergillosis CNS: Cryptococcus	A polyene antimicrobial: inserts into fungal cytoplasmic membrane causing altered membrane permeability and cell death	Nephrotoxicity Infusion reactions: chills, fevers, H/A Peripheral phlebitis	
nystatin	Candidiasis: mucocutaneous, GI, oral (thrush), vaginal		GI: N/V, diarrhea	Hypersensitivity to nystatin

**Liposomal Amphotericin B**

For patients who are intolerant of conventional amphotericin B therapy (e.g. renal impairment).

Table 32. Antifungals (continued)

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
IMIDAZOLES				
clotrimazole (Canesten®)	Oral and vulvovaginal candidiasis Dermatomycoses	All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability	Pruritis, skin irritation	Hypersensitivity to clotrimazole
miconazole (Monistat®, Micozole®)	Vulvovaginal candidiasis Dermatomycoses		Vaginal burning Nausea + vomiting	Hypersensitivity to miconazole
ketoconazole (Apo ketoconazole®, Nizoral®)	Dermatomycoses Seborrheic dermatitis		Pruritis, skin irritation GI nonspecific	Hypersensitivity to ketoconazole, cross-sensitivity with other azoles possible Hepatic dysfunction Pregnant women or those that may become pregnant
TRIAZOLES				
fluconazole (Diflucan®)	Candidiasis Cryptococcal meningitis (step-down therapy)	All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability	Elevated liver enzymes GI nonspecific	Hypersensitivity to fluconazole, cross-sensitivity with other azoles unknown Concurrent use of terfenadine if dose of fluconazole >400 mg
itraconazole (Sporanox®)	Candidiasis Systemic mycoses: histoplasmosis, blastomycosis, sporotrichosis, onychomycoses, coccidioidomycosis		Elevated liver enzymes Rash GI nonspecific	Hypersensitivity to itraconazole, cross-sensitivity with other azoles unknown Severe ventricular dysfunction
voriconazole (Vfend®)	Aspergillosis Candidiasis		Visual disturbance (30%) Hepatotoxicity Rash	Hypersensitivity to voriconazole, cross-sensitivity with other azoles unknown May avoid or alter doses if co-administered with other CYP3A4 substrates, rifampin, carbamazepine, long-acting barbiturates, ritonavir, efavirenz, sirolimus, rifabutin, ergot alkaloids fluconazole >400 mg
posaconazole (Posanol®, Noxafil®)	Candidiasis Aspergillosis		GI nonspecific Elevated liver enzymes Headache	Hypersensitivity to posaconazole, coadministration of cisapride, ergot alkaloids, pimozide, quinidine, or sirolimus
ALLYLAMINES				
terbinafine (Lamisil®)	Dermatomycoses Onychomycoses	Inhibits enzyme needed for ergosterol synthesis	Rash, local irritation GI nonspecific	Hypersensitivity to terbinafine
ECHINOCANDINS				
caspofungin	Failed aspergillosis, candidemia, febrile neutropenia Azole-resistant Candida	Inhibits 1-3 beta-glycan synthesis (needed for fungal cell wall)	Hepatotoxicity	

Antiparasitics

Table 33. Antiparasitics

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
ANTIMALARIALS				
chloroquine	Malaria: treatment of erythrocytic phase of all five species of <i>Plasmodium</i> that infect humans Note high resistance of <i>P. falciparum</i> and <i>P. vivax</i> in certain geographic areas	Inhibits parasite heme polymerase	CNS: blurred vision, retinopathy, dizziness GI nonspecific (rare with prophylaxis)	Hypersensitivity to chloroquine or other 4-aminoquinoline Retinal or visual field changes due to 4-aminoquinoline
quinine	Malaria: treatment of all four species of <i>Plasmodium</i> that infect humans, including chloroquine-resistant <i>P. falciparum</i>		Cinchonism: ears (tinnitus, vertigo), eyes (visual disturbance), GI (N/V diarrhea), CNS (H/A, fever) Hypoglycemia	Hypersensitivity to quinine, may have cross-sensitivity with quinidine Patients with G6PD deficiency, tinnitus, optic neuritis, hypoglycemia, history of blackwater fever or thrombocytopenic purpura due to quinine use
mefloquine (Lariam®)	Malaria: treatment and prophylaxis of all four species of <i>Plasmodium</i> that infect humans		CNS/Psych: irritability, nightmares, psychoses, suicide, depression, seizures, H/A	History of seizures, psychosis, severe anxiety or depression
primaquine	Malaria: treatment of liver hypnozoites of <i>P. vivax</i> and <i>P. ovale</i> . Prophylaxis of all <i>Plasmodium</i> spp. <i>Pneumocystis carinii</i> (with clindamycin)	Interferes with mitochondrial function	Hemolytic anemia in G6PD deficient GI upset (take with food)	GI nonspecific G6PD deficiency Concurrent or recent use of quinacrine Pregnancy
atovaquone/proguanil (Malarone®)	Malaria: treatment and prophylaxis of <i>P. falciparum</i>	Inhibits mitochondrial electron transport and dihydrofolate reductase	N/V, anorexia, diarrhea, abdo pain (take with food)	Hypersensitivity to atovaquone or proguanil Severe renal impairment
OTHER ANTI-PROTOZOAL				
iodoquinol (Diodoquin®)	Amebiasis: <i>E. histolytica</i> , <i>Dientamoeba fragilis</i> , <i>Balantidium coli</i> , <i>Blastocystis hominis</i>	Contact amoebicide that acts in intestinal lumen by uncertain mechanism	GI: N/V, diarrhea, abdo pain CNS: H/A, seizures, encephalitis	Hypersensitivity to any 8-hydroxy-quinoline or iodine Patients with hepatic damage or optic neuropathy
metronidazole	<i>Amoebas</i> , <i>T. vaginalis</i> , <i>giardiasis</i>	See Antibiotics, ID49		
nitazoxanide	<i>Cryptosporidium</i> , <i>giardiasis</i>	Interferes with parasite anaerobic metabolism	N/V, diarrhea, abdo pain, headache	Hypersensitivity to nitazoxanide
ANTI-HELMINTH				
praziquantel	<i>Schistosomiasis</i> and other flukes Tapeworms	Increases Ca permeability of helminth cell membrane, causing paralysis and detachment	N/V, fever, dizziness	Ocular cysticercosis
albendazole	Intestinal roundworms <i>Neurocysticercosis</i> <i>Microsporidiosis</i> <i>Echinococcus</i> → Hydatid disease	Inhibits glucose uptake into susceptible parasites	Elevated liver enzymes Alopecia GI nonspecific Agranulocytosis	Pregnancy
mebendazole (Vermox®)	Intestinal roundworms: - pinworm - whipworm - hookworm - roundworm	Inhibits microtubules formation and glucose uptake	GI nonspecific	Pregnancy, infants
ivermectin	<i>Strongyloidiasis</i> <i>Onchocerciasis</i>	Interferes with polarization of nerve and muscles cells in susceptible parasites leading to paralysis	Nausea, bloating, diarrhea, myalgias, lightheadedness, headache	Hypersensitivity to ivermectin
diethylcarbamazine	<i>Wuchereria bancrofti</i> <i>Loa loa</i>		Anorexia, N/V, headache, drowsiness, encephalitis, retinal haemorrhage Mazzotti reaction if coinfectd with onchocerciasis	Pregnancy

A Simplified Look at Antibiotics

1. Penicillins (most *Streptococcus*, some *N. meningitidis*, many oral anaerobes except *B. fragilis*)

- penicillin G/penicillin V
- ampicillin/amoxicillin (+ *Enterococcus*)
- benzathine pen G (syphilis)
- piperacillin (+ *Enterococcus*, *Pseudomonas*, GN coverage)
 - piperacillin-tazobactam
- cloxacillin (+ MSSA)

2. Cephalosporins (PO/IV)

- 1st generation: cephalexin/cefazolin (mostly GP, some GN)
- 2nd generation: cefuroxime/cefuroxime, cefoxitin, cefotetan (some GP and some GN)
- 3rd generation: cefixime/cefotaxime, ceftriaxone (good *Streptococcal* coverage, mostly GN) and ceftazidime (no GP, mostly GN, *Pseudomonas*)
- 4th generation: --/cefepime (most GP, most GN, *Pseudomonas*)

3. Aminoglycosides (GN aerobic bacilli)

- gentamicin
- tobramycin (+ *Pseudomonas*)
- amikacin (+ *Pseudomonas*)

4. Macrolides (GP, *Hemophilus*, *Legionella* and atypicals)

- erythromycin
- clarithromycin
- azithromycin

5. Fluoroquinolones (GN)

- ciprofloxacin (+ *Pseudomonas*)
- ofloxacin
- norfloxacin (for UTI only)
 - resp. fluoroquinolones: (some GP, GN, “atypicals”, *Legionella*, *Mycoplasma*, *Chlamydophila*)
- levofloxacin
- moxifloxacin (+ anaerobes)

6. Carbapenems (broad coverage: GP, GN and anaerobes)

- imipenem (+ *Pseudomonas*)
- meropenem (+ *Pseudomonas*)
- ertapenem

7. Others

- doxycycline/tetracycline (syphilis, *Chlamydophila*)
- vancomycin (all GP and *C. difficile* – the oral form)
- linezolid (for resistant GP infections)
- clindamycin (most GP aerobes, GN anaerobes)
- TMP/SMX (GN aerobes, *Pneumocystis*)
- nitrofurantoin (GN bacilli, *S. saprophyticus*, *Enterococcus*)
- metronidazole (anaerobes, *C. difficile*, *Trichomonas*, *Entamoeba*)

- **treatment for *C. Difficile*:** metronidazole OR oral vancomycin; consider both in serious infection

Quick Reference: Common Infections and their Antibiotic Management

Table 34. Common Infections and their Antibiotic Management

INFECTION	BACTERIA	ANTIBIOTIC
RESPIRATORY		
Pneumonia		
• Community-acquired	<i>S. pneumoniae</i> , <i>H. influenzae</i> B, <i>M. catarrhalis</i> , <i>Mycoplasma</i> , <i>Chlamydia</i> , <i>S. aureus</i>	Outpatient: macrolide OR doxycycline OR resp. fluoroquinolone Hospitalized: 3rd gen. cep. + macrolide OR resp. fluoroquinolone
• Hospital-acquired:	GNR (<i>Pseudomonas</i> , <i>Klebsiella</i> , <i>E. coli</i> , <i>Enterobacter</i>)	(piperacillin OR 3rd gen. cep OR fluoroquinolone OR carbapenem) + vancomycin
Tuberculosis	<i>Mycobacterium tuberculosis</i>	rifampin + isoniazid + pyrazinamide + ethambutol
UTI		
Cystitis	KEEP ² S ²	TMP/SMX OR fluoroquinolone OR nitrofurantoin
Pyelonephritis	KEEP ² S ²	TMP/SMX OR 3rd gen. cep OR ciprofloxacin
Urethritis	<i>Neisseria</i>	ceftriaxone
	<i>Chlamydia</i>	azithromycin OR doxycycline
SOFT TISSUE		
Cellulitis	MSSA, β -hemolytic strep	cloxacillin OR cephalexin
Necrotizing Fasciitis	Type I: polymicrobial (GNR)	carbapenem OR (3rd gen. cep + β -lactam/ β -lactamase inhibitor + metronidazole)
	Type II: β -hemolytic strep	penicillin + clindamycin
BONE		
Osteomyelitis	MSSA	cloxacillin OR cefazolin
Diabetic Foot		
• Mild	MSSA, <i>Streptococcus</i> spp.	TMP/SMX-DS + metronidazole
• Chronic non-limb/life-threatening	polymicrobial (aerobes + anaerobes)	ciprofloxacin + clindamycin
• Life-threatening	polymicrobial	imipenem or piperacin-tazobactam
Septic Arthritis	<i>N. gonorrhoeae</i> (sexually active adults) <i>S. aureus</i> , <i>S. pyogenes</i>	ceftriaxone or ampicillin
Meningitis	<i>S. pneumo</i> , <i>N. meningitidis</i> , <i>H. influenza</i>	ceftriaxone + vancomycin (+ ampicillin for <i>Listeria</i>)
Bacterial Endocarditis		
• Native valve	<i>S. viridans</i> , <i>S. aureus</i> , <i>Enterococcus</i>	vancomycin + gentamicin

KEEP²S² = *Klebsiella*, *E. Coli*, *Enterococci*, *Proteus mirabilis*, *Pseudomonas*, *S. saprophyticus*, *S. fecalis*

References

Principles of Microbiology

Andreoli TE. Cecil Essentials of Medicine. 6th edition. W.B. Saunders Company; 2003.
 Hawley, LB. High Yield Microbiology and Infectious Diseases. Lippincott Williams & Wilkins; 2000.
 Mandell, GL, Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease. 6th Edition. Churchill Livingstone 2005.
 Levinson, Warren and Ernest Jawetz. Medical Microbiology and Immunology: Examination and Board Review. 7th Edition. McGraw Hill 2003.
 McGraw Hill. Harrison's Online. Website: HYPERLINK "<http://www.harrisonsonline.com>" <http://www.harrisonsonline.com>
 Schaechter M, Engleberg N, Eisenstein B, Medoff G. Mechanisms of Microbial Disease. Lippincott Williams & Wilkins; 1998.

Neurological Infections

Peterson LR, et al. West Nile Virus. JAMA. 2003; 290(4): 524-527.
 Roberts L. Mosquitos and Disease. Science. 2002; 298(5591): 82-3.

Respiratory Infections

Dunbar LM, Wunderink RG, Habib MP, Smith LG, Tenenber AM, Khashab MM, Wiesinger BA, Xiang JX, Zadeikis N, and Kahn JB. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. Clinical Infectious Disease; 2003; 37:752-60.
 Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America / American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. CID 2007, 44(Suppl 2): S27-S72.

Cardiac Infections

Li JS, et al. Proposed modifications to the Duke Criteria for the Diagnosis.
 Wilson W, et al. Prevention of Infective Endocarditis. Guidelines from the American Heart Association. Circulation 2007 Apr 19; [Epub ahead of print].

Gastrointestinal Infections

American Academy of Pediatrics. Pickering LK, Baker CJ, Long SS, McMillan JA, eds. Red Book: 2006 Report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006.

Bone and Joint Infections

Butalia S, Palda VA, Sargeant RJ, Detsky AS, and Mourad, O. Does this patient with diabetes have osteomyelitis of the lower extremity? JAMA; 2008; 299(7):806-13.
 Hellman DB, and Imboden JB. Musculoskeletal and Immunologic disorders. In: Current Medical Diagnosis & Treatment. 2010. Edited by McPhee SJ and Papadakis M.A. The McGraw-Hill Companies, Inc.
 Gilbert DN, Moellering RC, Eliopoulos GM, and Sande MA. The Sanford Guide to Antimicrobial Therapy 2008, 38th ed.
 Margaretten ME, Kohlves J, Moore D, and Bent S. Does this adult patient have septic arthritis? JAMA. 2007;297:1478-1488.

Systemic Infections

Alejandria MM, Lansang MA, Dans LF, Mantaring JBV. Intravenous immunoglobulin for treating sepsis and septic shock (Cochrane Review). In: The Cochrane Library, Issue 2, 2002. Oxford: Update Software.
 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. SO – Crit Care Med 1992 Jun;20(6):864-74.
 Bernard GR, Vincent JL, LaTerre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. NEJM 2001;344:699-709.
 Fourrier F, Chopin C, Goumand J, et al. Septic shock, multiple organ failure, and disseminated intravascular coagulation: compared patterns of antithrombin III, protein C and protein S deficiencies. Chest 1992;101:816-23.
 Smieja MJ, Marchetti CA, Cook DJ, Smail FM (2002). Isoniazid for preventing tuberculosis in non-HIV infected persons (Cochrane Review). In: The Cochrane Library, Issue 2. Oxford: Update Software.
 Steere AC. Lyme disease. New England Journal of Medicine. 2001. July 12; 345(2):115-25.
 Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection Am J Respir Crit Care Med, Vol 161. pp.S221-S247, 2000.
 Tuberculosis: selected series. Mechanisms of microbial disease. CMAJ. 1999. 160.

HIV and AIDS

2006 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Available at: HYPERLINK "<http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentsGL.pdf>" <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentsGL.pdf>
 Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons – 2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. Available at: HYPERLINK "<http://aidsinfo.nih.gov/ContentFiles/OIpreventionGL.pdf>" <http://aidsinfo.nih.gov/ContentFiles/OIpreventionGL.pdf>
 Hammer SM, Saag MS, Schechter et al. Treatment for adult HIV Infection: 2006 recommendations of the International AIDS Society – USA Panel. JAMA 2006; 296(7): 827-43.
 Hladik F and McElrath MJ. Setting the stage: host invasion by HIV. Nat Rev Immunology. 2008;8:447-457.
 Moylett EH and Shearer WT. HIV: clinical manifestations. J Allergy Clin Immunol 2002;110:3-16.
 Public Health Agency of Canada. HIV and AIDS in Canada. Selected Surveillance Tables to June 30, 2007. Surveillance and Risk Assessment Division, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada, 2007. (HYPERLINK "<http://www.phac-aspc.gc.ca/aids-sida/publication/index.html>" \ "surveillance" <http://www.phac-aspc.gc.ca/aids-sida/publication/index.html#surveillance>)
 WHO. WHO AIDS Epidemic Update 2007. HYPERLINK "http://data.unaids.org/pub/EPISlides/2007/2007_epiupdate_en.pdf" http://data.unaids.org/pub/EPISlides/2007/2007_epiupdate_en.pdf
 Wilkinson D (2002). Drugs for preventing tuberculosis in HIV infected persons (Cochrane Review). In: The Cochrane Library, Issue 2. Oxford: Update Software.

Parasitic Infections

Center for Disease Control & Prevention. DPDx: Identification and Diagnosis of Parasites of Public Health Concern.
 Website: HYPERLINK "<http://www.dpd.cdc.gov/dpdx/Default.htm>" <http://www.dpd.cdc.gov/dpdx/Default.htm>
 Croft MA and Jacquerioz FA. Drugs for preventing malaria in travelers. Cochrane Database Syst Rev 2009; (4): CD006491.

Infections in the Immunocompromised Host

Hughes WT, et al. Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer. CID 2002; 34:731-757.

Fever of Unknown Origin

Knockaert DC, et al. Fever of Unknown Origin in adults: 40 years on. Journal of Internal Medicine. 2003; 253: 263-275.
 Spira AM. Assessment of traveller's who return home ill. Lancet. 2003; 361(9367):1459-69.

MRSA

American Academy of Pediatrics. Staphylococcal Infections. In: Pickering LK, Baker CJ, Long SS, McMillan JA, eds. Red Book: 2006 Report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006.
 Simor AE, Ofner-Agostini M, Gravel D, Vania M, Paton S, McGeer A, Bryce E, Loeb M, Mulvey M, Canadian Nosocomial Infection Surveillance Program (CNISP). Surveillance for Methicillin-Resistant Staphylococcus aureus in Canadian Hospitals – A Report Update from the Canadian Nosocomial Infection Surveillance Program. CDR 2005; 31(3):1-7.
 Simor AE, Phillips E, McGeer A, Konvalinka A, Loeb M, Devlin HR, Kiss A. Randomized controlled trial of chlorhexidine gluconate for washing, intranasal mupirocin, and rifampin and doxycycline versus no treatment for the eradication of methicillin-resistant Staphylococcus aureus colonization. Clin Infect Dis. 2007 Jan 15;44(2):178-85.

Antimicrobials

e-CPS. Canadian Pharmacists Association. 2008. Available: HYPERLINK "<http://e-cps.pharmacists.ca>" <http://e-cps.pharmacists.ca>
 MD consult drugs online website: HYPERLINK "<http://home.mdconsult.com/das/drugs/>" <http://home.mdconsult.com/das/drugs/>
 Schlossberg, D, Ed. Current Therapy of Infectious Disease. 2nd Edition. Mosby Inc, St Louis, Missouri, 2001.

Katie Connolly, Melanie Ostreicher and Elissa Rennert-May, chapter editors

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Basic Anatomy Review

Anatomy of the Kidney

- see Urology, U2

Renal Structure and Function

The Nephron

- basic structural and functional unit of the kidney, approximately 1 million per kidney
- 2 main components: glomerulus and attached renal tubule (Figure 1)
- direction of blood flow: afferent arteriole → glomerular capillaries → efferent arteriole → vasa recta (the capillaries surrounding the tubules) → renal venules

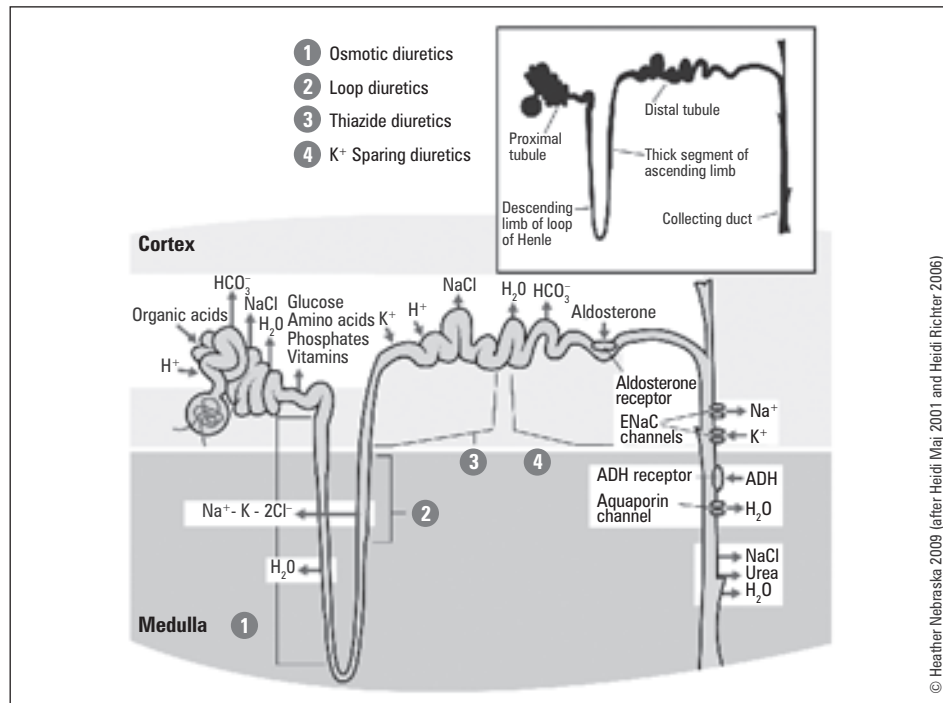


Figure 1. Nephron Components

Table 1. Major Functions of the Kidneys

Function	Mechanism	Affected Elements
1. Waste Excretion	Glomerular filtration Tubular secretion Tubular catabolism	Excretion of nitrogenous products of protein metabolism (urea, Cr) Excretion of organic acids (urate) and organic bases (Cr) Breakdown and excretion of drugs (antibiotics, diuretics) and peptide hormones (most pituitary hormones, insulin, glucagon)
2. Electrolyte Balance	Tubular NaCl and water reabsorption Tubular K secretion Tubular H secretion HCO ₃ synthesis and reabsorption Tubular Ca, Mg, PO ₄ transport	Controls volume status and osmolar balance Controls potassium concentration Acid-base balance Acid-base balance Alters Ca, Mg, PO ₄ homeostasis
3. Hormonal Synthesis	Erythropoietin production (cortex) Vitamin D activation [25(OH)D → 1,25(OH)D] Renin production (JG apparatus)	Red blood cell production Calcium homeostasis Alters vascular resistance and aldosterone secretion
4. Blood Pressure Regulation	Na excretion Renin production	Alters ECF volume Alters vascular resistance
5. Glucose Homeostasis	Gluconeogenesis (from lactate, pyruvate and amino acids)	Glucose supply maintained in prolonged starvation

The Glomerulus

- site where blood constituents are filtered through to the kidney tubules for excretion or reabsorption
- consists of following cell types
 1. capillary endothelial cells and podocytes
 - ♦ support the glomerular basement membrane (GBM) and form the plasma filtration apparatus
 2. mesangial cells
 - ♦ have contractile properties and produce vasoactive substances to help control blood flow
 3. parietal epithelium
 - ♦ covers the interior of Bowman's capsule
- filtration occurs across the GBM into Bowman's space (Figure 2)
- filtration barrier: consists of capillary endothelium, GBM, podocyte filtration slits
 - particles are selectively filtered by size (<60 kDa) and charge (negative charge repelled)

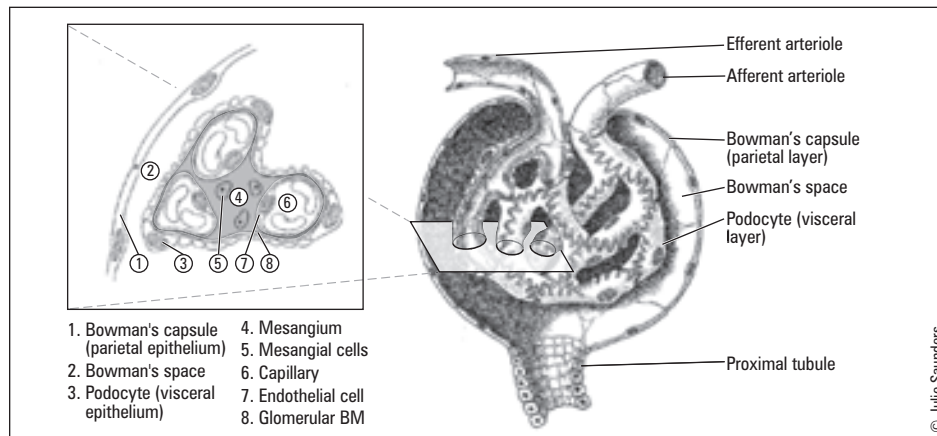


Figure 2. The Glomerulus

The Renal Tubules

- reabsorption and secretion occur between the renal tubules and vasa recta until tubular fluid is transformed into urine for excretion
- each anatomic segment of the nephron has unique characteristics and specialized functions that enable selective transport of solutes and water
 - proximal tubule
 - ♦ responsible for reabsorbing ~60% of filtered NaCl and water, as well as ~90% of filtered bicarbonate and most critical nutrients such as glucose and amino acids
 - loop of Henle
 - ♦ consists of three major segments by cellular morphology and location: descending thin limb, ascending thin limb, and ascending thick limb
 - ♦ important role in urinary concentrating ability by contributing to the generation of a hypertonic medullary interstitium
 - ♦ contributes to reabsorption of calcium and magnesium ions
 - distal convoluted tubule
 - ♦ reabsorbs ~5% of the filtered NaCl
 - ♦ composed of a tight epithelium with little water permeability
 - ♦ regulates pH by absorbing bicarbonate and secreting H
 - ♦ reabsorbs calcium in response to parathyroid hormone
 - collecting duct
 - ♦ regulates the final composition of the urine
 - ♦ important for hormonal regulation of salt and water balance (water reabsorption governed by antidiuretic hormone)
 - ♦ reabsorption of sodium and secretion of potassium at cortical collecting duct regulated by aldosterone

Renal Hemodynamics

- Renal Blood Flow (RBF) of Renal Plasma Flow (RPF): 20% of cardiac output = 1000 mL/min
- Glomerular Filtration Rate (GFR)
 - the rate of fluid transfer between glomerular capillaries and Bowman's space
 - 120 mL/min in healthy adult = 173 L/day, of which 99% is reabsorbed, giving a daily urine output of 1.0-1.5 L
 - highest in early adulthood, decreasing thereafter



Glomerular Filtration Rate

$$GFR = K_f (\Delta P - \Delta \Pi)$$

K_f = ultrafiltration coefficient

ΔP = hydrostatic pressure

$\Delta \Pi$ = osmotic pressure

Net outward pressure

- renal autoregulation maintains a constant GFR over a range of mean arterial pressures (70 to 180 mmHg). 2 mechanisms of autoregulation:
 - myogenic mechanism: release of vasoactive factors in response to alterations in perfusion pressure. E.g. rise in perfusion pressure causes afferent arteriolar constriction, leading to a decrease in GFR
 - tubuloglomerular feedback: changes in [Na] delivery to macula densa lead to afferent arteriolar tone (increased delivery causes afferent constriction)
- Filtration Fraction (FF)
 - percentage of RPF filtered across the glomeruli
 - expressed as a ratio: $FF = GFR/RPF$, normal = 0.2 or 20%
 - angiotensin II (A_{II}) causes constriction of renal efferent arterioles which increases FF thereby maintaining GFR
- renin is released from juxtaglomerular apparatus in response to decreased RPF

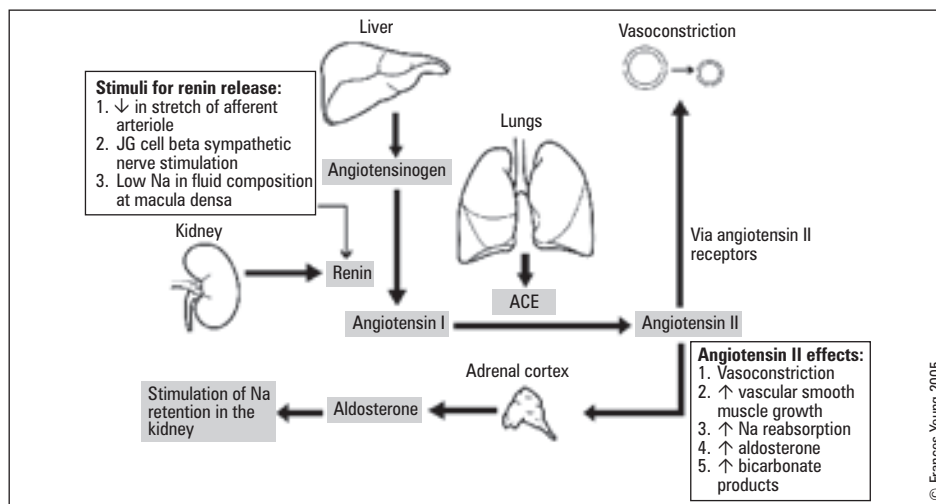


Figure 3. Stimuli for Renin Release

Differential Diagnoses of Common Presentations

Azotemia

Definition

- higher urea and Cr are usually caused by inability of the kidney to excrete urea, Cr and other nitrogen-containing compounds in the blood

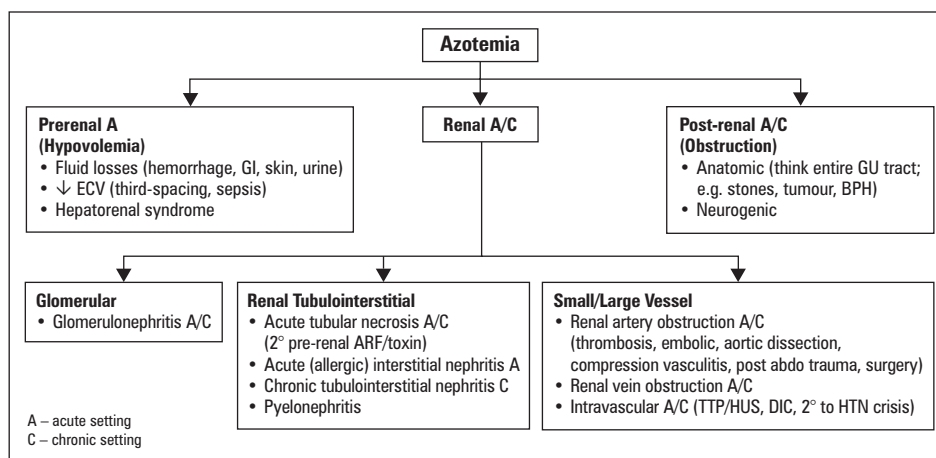


Figure 4. Classification of Azotemia

Proteinuria

Definition

- 24-hour urine protein: gold standard to assess degree of proteinuria (see Table 2)
- urine albumin-to-creatinine ratio (ACR): used to screen for diabetic nephropathy
 - Microalbuminuria
 - ♦ defined as ACR ≥ 2.8 mg/mmol (female) or ≥ 2.0 mg/mmol (male)
 - ♦ marker of vascular endothelial function
 - ♦ an important prognostic marker for kidney disease in diabetes and hypertension (see *Diabetes and the Kidney*, NP34)
 - an elevated ACR ≥ 2.0 or 2.8 mg/mmol is the earliest sign of diabetic nephropathy
- composition of normal total urine protein
 - 60% filtered plasma protein: 50% albumin, 15% Ig, 25% other
 - 40% Tamm-Horsfall mucoprotein secreted from tubular cells

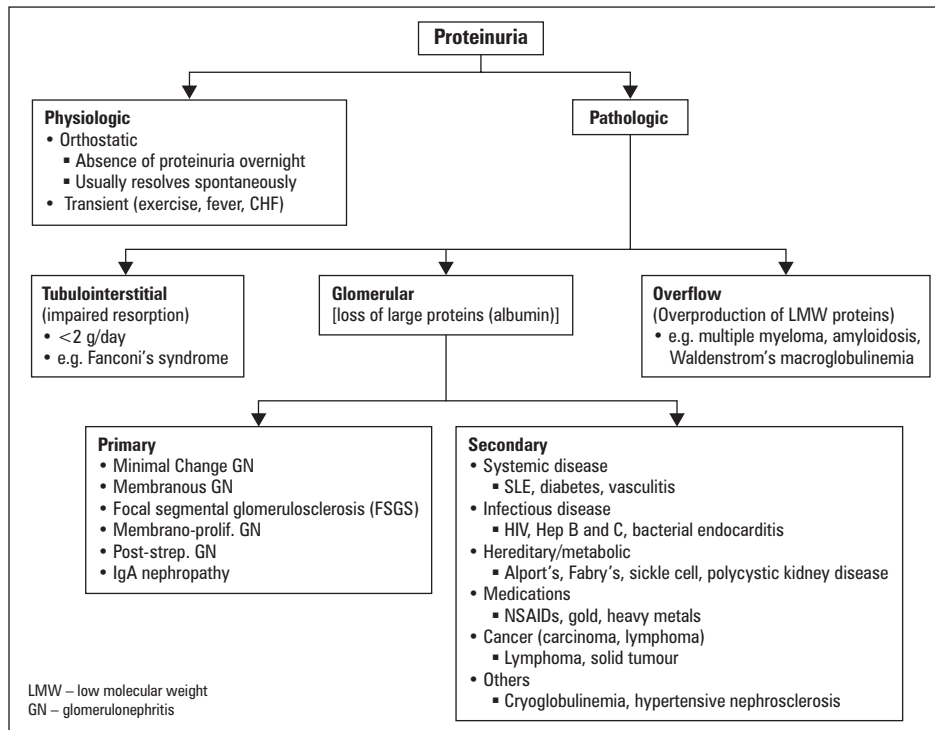


Figure 5. Classification of Proteinuria

Table 2. Daily Excretion of Protein

Daily Excretion	Meaning
<150 mg total protein (and <30 mg albumin)	Normal
30-300 mg albumin	Microalbuminuria
>3500 mg total protein	Nephrotic range proteinuria
Variable amount of proteinuria	Can be seen with glomerular disease; i.e. mild glomerular disease can lead to a mild degree of proteinuria, proliferative lesions may also be associated with some degree of proteinuria
Up to 2000 mg per day	Possible tubular disease because of failure to reabsorb filtered proteins

Investigations

- urine R&M, C&S, urea, Cr
- further workup (if degree of proteinuria >0.5 g/day, casts and/or hematuria)
 - CBC, glucose, electrolytes, 24-hr urine protein and Cr
 - urine and serum immunoelectrophoresis, abdominal/pelvic ultrasound
 - serology: ANA, RF, p-ANCA, c-ANCA, Hep B, Hep C, HIV, ASOT
- indications for nephrology referral
 - ACR >30-1000 mg/mmol
 - nephrotic syndrome: marked proteinuria >3.5 g/1.73m²/day with hypoalbuminemia (<35 g/L)



PATHOLOGIC PROTEINURIA

- 1. Tubulointerstitial**
 - Normally low molecular weight (LMW) proteins (<60 kD) pass through glomerular filtration barrier and are reabsorbed in proximal tubule
 - Proximal tubule dysfunction causes impaired reabsorption and increased excretion of LMW proteins
 - Albumin (>60 kD) is NOT affected. Thus, edema is partly secondary to salt and water retention
- 2. Glomerular**
 - Normally, the filtration barrier is selectively permeable to SIZE (<60 kD) and CHARGE (repels negative particles). Thus, albumin is NOT filtered through a normal glomerulus
 - Damage to any component of the glomerular filtration barrier results in loss of albumin and other high MW proteins. Thus, edema is secondary to hypoalbuminemia (low oncotic pressure), but also due to enhanced renal tubular reabsorption of filtered sodium and water (mechanism uncertain)
- 3. Overflow**
 - Increased production of LMW proteins which exceeds the reabsorptive capacity of the proximal tubule
 - Plasma cell dyscrasias: produce light chain Ig (multiple myeloma, Waldenstrom's macroglobulinemia, monoclonal gammopathy of undetermined significance)



Hematuria

Definition

- presence of blood or RBCs in urine
 - gross hematuria: pink, red, or tea-coloured urine
 - ♦ in gross hematuria, the urine should be centrifuged
 - ♦ it is hematuria only if the sediment is red. If the supernatant is red, test for heme with a dipstick
 - if +ve for heme: myoglobinuria or hemoglobinuria
 - if -ve for heme: pseudohematuria. Consider medications (e.g. rifampin), food dyes (e.g. beets) or metabolites (e.g. porphyria)
 - microscopic hematuria: normal coloured urine, >2-3 RBCs/HPF on microscopy

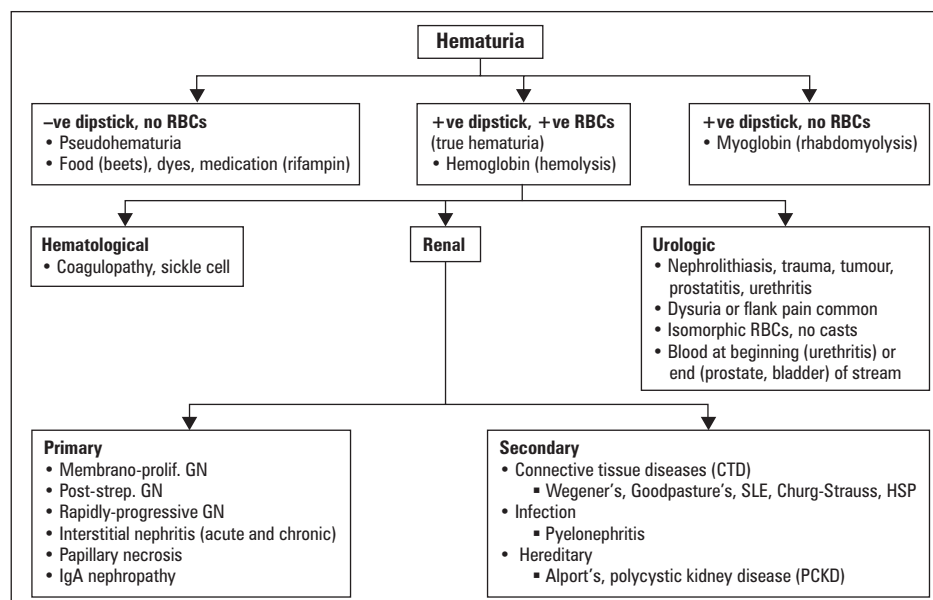


Figure 6. An Approach to Hematuria

Investigations for Hematuria

- Hx and Px: family history of nephrolithiasis, hearing loss (Alport's), cerebral aneurysm (PCKD), diet, recent URTI, irritative and obstructive urinary symptoms (UTI)
- urine R&M, C&S, urea, Cr
- 24-hr urine stone workup: calcium, oxalate, citrate, magnesium, uric acid, cysteine
- further workup (if casts and/or proteinuria): CBC, electrolytes, 24-hr urine protein and Cr, serology (ANA, RF, C3, C4, p-ANCA, c-ANCA, ASOT), abdo/pelvic ultrasound, cystoscopy ± urology consult

Assessment of Renal Function

Measurement of Renal Function

- Glomerular Filtration Rate (GFR) = rate of filtration of plasma by the glomeruli
- most renal functions decline in parallel with a decrease in GFR
- GFR is often estimated using serum creatinine concentrations [Cr]
- creatinine (Cr) is a metabolite of creatine (intermediate in muscle energy metabolism)
- Cr is freely filtered at the glomerulus with no tubular reabsorption and minimal secretion (10%)
- rate of production determined by muscle mass
- Cr excreted ≈ Cr filtered (at steady state)

Ways to Estimate GFR

1. Calculate creatinine clearance (CrCl)

- calculation provides reasonable estimate of GFR
- measure plasma [Cr], 24-hr urine volume and urine [Cr]
 - $GFR = \frac{\text{urine [Cr]} \times \text{urine volume in mL}}{\text{plasma [Cr]} \times \text{duration of urine collection in minutes}}$
- two major errors limiting the accuracy of CrCl
 - increasing Cr secretion can overestimate true GFR, particularly in azotemic patients
 - incomplete urine collection can underestimate true GFR; over-collection of urine overestimates it



$$Cr_{\text{filtered}} = Cr_{\text{excreted}}$$

$$[Cr]_{\text{plasma}} \times GFR = [Cr]_{\text{urine}} \times \text{urine flow rate (mL/min)}$$

$$GFR = \frac{[Cr]_{\text{urine}} \times \text{urine flow rate}}{[Cr]_{\text{plasma}}}$$



There is an inverse relationship between serum Cr concentration and CrCl at steady state.

2. Cockcroft-Gault formula

- serum Cr used along with age, gender and weight (kg) to estimate GFR (see sidebar)
 - normal range is >90 mL/min (>1.5 mL/s)

3. MDRD (Modification of Diet in Renal Disease) formula

- most common way in which GFR is estimated
- complex formula incorporating age, gender, serum Cr, African descent
- GFR is reported as mL/min/1.73m² body surface area

Limitations of Using Serum Cr Measurements

- must be in steady state
 - constant GFR and rate of production of Cr from muscles
 - sudden injury may reduce GFR substantially, but it takes time for Cr to accumulate and then re-establish steady state
- GFR must fall substantially before plasma [Cr] rises above normal laboratory range
 - with progressive renal failure, remaining nephrons compensate with hyperfiltration
 - GFR is relatively preserved despite significant structural damage
- plasma [Cr] is influenced by the rate of Cr production
 - lower production with smaller muscle mass (i.e. female, elderly, low weight)
 - e.g. consider plasma [Cr] of 100 µmol/L (1.13 mg/dL) in both of these patients
 - 20 year-old man who weighs 100 kg, GFR = 144 mL/min
 - 80 year-old woman who weighs 50 kg, GFR = 30.6 mL/min
- contribution of tubular secretion to Cr excretion is increased when GFR is low
 - CrCl overestimates GFR
 - certain drugs (cimetidine, trimethoprim) interfere with Cr secretion
- errors in Cr measurement
 - very high bilirubin level causes [Cr] to be falsely low
 - acetoacetate (a ketone body) and certain drugs (cefexitin) create falsely high [Cr]

Measurement of Urea Concentration

- urea is the major end product of protein metabolism
- plasma urea concentration is a measurement of renal function but should not be used alone as it is modified by a variety of factors
- urea production reflects dietary intake of protein and catabolic rate; increased protein intake or catabolism (sepsis, trauma, GI bleed) causes urea level to rise
- ECF volume depletion causes a rise in urea independent of GFR or plasma [Cr]
- in addition to filtration, a significant amount of urea is reabsorbed along the tubule
- reabsorption is increased in sodium-avid states such as ECF volume depletion
- typical ratio of urea to [Cr] in serum is 1:12 in Canadian units (using mmol/L for urea and µmol/L for Cr), and 14:1 in US units (urea expressed as BUN in mg/dL and Cr in mg/dL)

Urinalysis

- use dipstick in freshly voided urine specimen to assess the following:

1. Specific Gravity

- ratio of the mass of equal volumes of urine/H₂O
- normal range is 1.001 to 1.030
- values <1.010 reflect dilute urine, values >1.020 reflect concentrated urine
- value usually 1.010 in end stage renal disease (isosthenuria)

2. pH

- urine pH is normally between 4.5-7.0; if persistently alkaline, consider:
 - renal tubular acidosis
 - UTI with urease-producing bacteria (e.g. *Proteus*)

3. Glucose

- freely filtered at glomerulus and reabsorbed in proximal tubule
- causes of glucosuria include
 - hyperglycemia >9-11 mmol/L (>160-200 mg/dL) leads to filtration that exceeds tubular reabsorption capacity
 - increased GFR (e.g. pregnancy)
 - proximal tubule dysfunction (e.g. Fanconi's syndrome)

4. Protein

- dipstick only detects albumin; other proteins (e.g. Bence-Jones, Ig, Tamm-Horsfall) may be missed
- microalbuminuria (defined as 30-300 mg/day) is not detected by standard dipstick (see *Diabetes and the Kidney*, NP34)
- sulfosalicylic acid detects all protein in urine by precipitation
- gold standard: 24-hr urine collection for total protein

**Cockcroft-Gault Formula**

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 1.2}{[\text{Cr}]_{\text{plasma}} (\text{umol/L})} \times 0.85 \text{ in women}$$

**Clinical Settings in which Urea Level is Affected Independent of Renal Function****Disproportionate increase in Urea**

Volume depletion (prerenal azotemia)
GI hemorrhage
High protein diet
Sepsis
Catabolic state with tissue breakdown
Corticosteroid or cytotoxic agents

Disproportionate decrease in Urea

Low protein diet
Liver disease

**24 hour Urine Collection**

- Discard first morning specimen
 - Collect all subsequent urine for the next 24 hrs
 - Refrigerate between voids
 - Collect second morning specimen
- Clarity:** Cloudiness may indicate infection

Colour: usually pale yellow or amber, but may be colourless (diabetes insipidus, excess water intake), bright yellow (due to riboflavin ingestion or vitamin tablets), or dark yellow (concentrated urine in intravascular volume depletion)

**Estimating Urine Osmolality**

Last 2 digits of the specific gravity x 30
= urine osmolality approximately
e.g. specific gravity of 1.020
= 600 mOsm

5. Leukocyte Esterase

- enzyme found in WBC and detected by dipstick
- presence of WBCs indicates infection (e.g. UTI) or inflammation (e.g. AIN)

6. Nitrites

- nitrates in urine are converted by bacteria to nitrites
- high specificity, low sensitivity for UTI
- +ve dipstick for leukocyte esterase and nitrites is 94% specific for diagnosing a UTI

7. Ketones

- positive in alcoholic/diabetic ketoacidosis, prolonged starvation, fasting

8. Hemoglobin

- positive in hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis) and true hematuria (RBCs seen on microscopy)

Urine Microscopy

- centrifuge urine specimen for 3-5 minutes, discard supernatant, resuspend sediment and plate on slide
- shaking tube vigorously may disrupt casts

1. CELLS

Erythrocytes

- normal range = 2-3 RBCs per high power field (HPF)
- hematuria = greater than 2-3 RBCs/HPF
- dysmorphic RBCs and/or RBC casts suggest glomerular bleeding (e.g. proliferative glomerulonephritis)
- isomorphic RBCs, no casts suggest extraglomerular bleeding (e.g. bladder Ca)

Leukocytes

- normal range = up to 3 WBCs/HPF
- pyuria = greater than 3 WBCs/HPF
- indicates inflammation or infection
- if persistent sterile pyuria present (i.e. negative culture), consider: chronic urethritis, prostatitis, interstitial nephritis, calculi, papillary necrosis, renal TB, viral infections

Eosinophils

- detected using Wright's or Hansel's stain (not affected by urine pH)
- consider allergic interstitial nephritis, atheroembolic disease

Oval Fat Bodies

- renal tubular cells filled with lipid droplets
- seen in heavy proteinuria (e.g. nephrotic syndrome)

2. CASTS

- cylindrical structures formed by intratubular precipitation of Tamm-Horsfall mucoprotein; cells may be trapped within the matrix of protein



Table 3. Interpretation of Casts

Hyaline casts	Physiologic (concentrated urine, fever, exercise)
Red blood cell casts	Glomerular bleeding (glomerulonephritis, vasculitis)
White blood cell casts	Infection (pyelonephritis) Inflammation (interstitial nephritis)
Pigmented granular casts (heme granular casts, muddy brown)	Acute tubular necrosis Glomerulonephritis, interstitial nephritis
Fatty casts	Heavy proteinuria (>3.5 g/day)

3. CRYSTALS

- uric acid – consider acid urine, hyperuricosuria (e.g. gout)
- calcium phosphate – alkaline urine
- calcium oxalate – consider hyperoxaluria, ethylene glycol poisoning
- sulfur – sulfa-containing antibiotics



Terminology

	Active Sediment	Bland Sediment
Any one or more of the following seen on microscopy	<ul style="list-style-type: none"> • Red cell casts • White cell casts • Muddy-brown granular or epithelial cell casts • >2 red cells per high power field (hpf) • >4 white cells per hpf 	<ul style="list-style-type: none"> • Hyaline casts • <2 red cells per hpf • <4 white cells per hpf • Small quantities of crystals • Small amount of bacteria
Significance	Highly suggestive of significant pathology, casts specifically suggest renal pathology	Reduced likelihood of significant pathology, but not ruled out

Urine Electrolytes

- can use to evaluate the source of an electrolyte abnormality or grossly assess tubular function
- commonly measure: Na, K, Cl, osmolality and pH
- no 'normal' values; electrolyte excretion depends on intake and current physiological state
- therefore results must be interpreted in the context of a patient's current state, e.g.
 1. ECF volume depletion: expect low urine [Na] (kidneys should be retaining Na)
 - ♦ a high urine [Na] in this setting suggests a renal problem or the action of a diuretic
 - ♦ urine [Na] <10 mmol/L suggests the patient is pre-renal
 2. daily urinary potassium excretion rate should be decreased (<20 mmol/d) in the setting of hypokalemia
 - ♦ if higher than 20 mmol/d, suggests renal etiology
- osmolality is useful to estimate the kidney's concentrating ability
- FE_{Na} refers to the fractional excretion of Na
 - $FE_{Na} = \text{Urine [Na]} \times \text{Plasma [Cr]} / (\text{Plasma [Na]} \times \text{Urine [Cr]})$
 - $FE_{Na} < 1\%$ suggests the pathology is prerenal



Fractional Excretion of Sodium

$$FE_{Na} = \frac{[\text{Na}]_{\text{Urine}} \times [\text{Cr}]_{\text{Plasma}}}{[\text{Na}]_{\text{Plasma}} \times [\text{Cr}]_{\text{Urine}}} \times 100$$

Many formulas used in nephrology are derived from the division of two fractions, each of which compare a urine and plasma concentration (e.g. $U_1/P_1 \div U_2/P_2$). In the case of FE_{Na} , it is $U_{Na}/P_{Na} \div U_{Cr}/P_{Cr}$, which then gives the above equation.

Examples of Common Urine Electrolyte Abnormalities

- high urine Na (>20 mmol/L) in the setting of acute renal failure: indicates renal disease vs. pre-renal
- high urine Na (>40 mmol/L) in the setting of hyponatremia: generally from causes such as diuretics, tubular disease (e.g. Bartter's syndrome), SIADH
- additionally, urine pH is useful to grossly assess renal acidification
 - "low" pH (<5.5) in the presence of low serum pH is an appropriate renal response
 - a high pH in this setting might indicate a renal acidification defect (e.g. RTA)

Electrolyte Disorders

Sodium Homeostasis

Introduction

- hyponatremia and hypernatremia are disorders of water balance
 - hyponatremia suggests too much water in the extracellular fluid relative to Na
 - hypernatremia is too little water in the extracellular fluid relative to Na
 - both can be associated with normal, decreased or increased total body Na
- solutes (such as Na, glucose, or urea) that cannot freely traverse the plasma membrane contribute to effective osmolality and induce transcellular shifts of water
 - water moves out of cells in response to increased ECF osmolality
 - water moves into cells in response to decreased ECF osmolality
- physiologically, ECF volume is determined by Na content, not Na concentration
 - Na deficiency leads to ECF volume contraction
 - Na excess leads to ECF volume expansion
- clinical signs and symptoms of hyponatremia and hypernatremia are secondary to cells (especially in the brain) shrinking (hypernatremia) or swelling (hyponatremia)



Common Electrolytes

Sodium (Na) 135-145 mmol/L

Potassium (K) 3.5-5 mmol/L

Chloride (Cl) 95-105 mmol/L

Bicarbonate (HCO_3) 18-23 mmol/L

Table 4. Clinical Assessment of ECF Volume (Total Body Na)

Fluid Compartment	Hypovolemic	Hypervolemic
Intravascular		
JVP	Decreased	Increased
Blood pressure	Orthostatic drop	Normal to increased
Auscultation of heart	Tachycardia	S3
Auscultation of lungs	Normal	Inspiratory crackles
Interstitial		
Skin turgor	Decreased	Normal/increased
Edema (dependent)	Absent	Present
Other		
Urine output	Decreased	Variable
Body weight	Decreased	Increased
Hct, serum protein	Increased	Decreased

Hyponatremia

- hyponatremia: serum $[Na] < 136$ mmol/L
- can be associated with increased, normal or decreased (most common) serum osmolality

Mechanisms of Hyponatremia

1. Hyponatremia despite dilute urine ($U_{osm} < 100$)

- expect urine to be dilute with hyponatremia (ADH should be suppressed)
- due to excessive water intake that overwhelms the kidneys' normal water excretion capacity
 - psychogenic polydipsia in psychiatric patients (e.g. schizophrenia)
- ability to excrete water is compromised in people with low solute excretion (particularly urea)
 - e.g. elderly women with "tea and toast" diet: low protein intake, low urea excretion

2. Hyponatremia with concentrated urine ($U_{osm} > 200$)

- if urine remains concentrated, ADH is acting when it should not be
- may be physiological (due to volume stimulus) or pathological (other reasons)
 - volume mediated ADH release can be due to true or effective volume depletion
 - ♦ causes of true volume depletion: losses from skin, GI, urine, blood or 3rd spacing
 - ♦ effective volume depletion: CHF and cirrhosis
 - pathological ADH release: SIADH and endocrine deficiency
 - ♦ SIADH – many causes including medications, lung disease, neurological disease, ectopic production, stress (pain, nausea, surgery); see Table 5
 - ♦ adrenal insufficiency (decreased volume and co-secretion of ADH and CRH)
 - ♦ hypothyroidism (decreased cardiac output, decreased GFR)

3. Hyponatremia with no (or minimal) urine

- advanced renal failure with oliguria may be associated with hyponatremia if the patient ingests even a moderate amount of dilute fluids



If the urine osmolality is unknown, assume the urine is hypoosmolar/dilute.

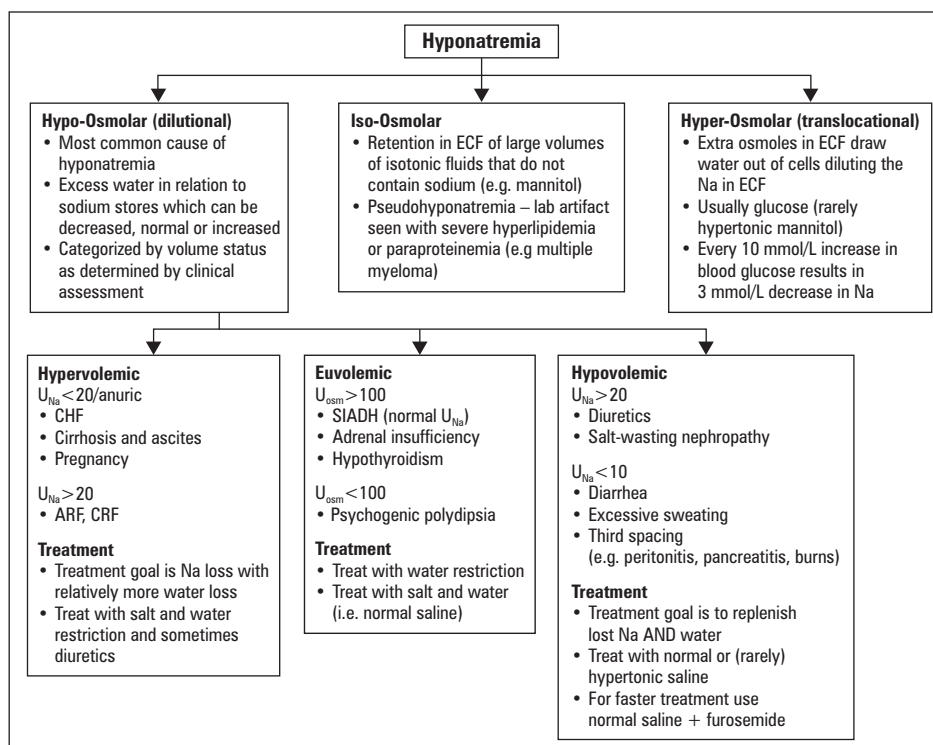


Figure 7. An Approach to Hyponatremia

Signs and Symptoms

- depend on degree of hyponatremia and more importantly, velocity of progression from onset
- acute hyponatremia (<24-48 hours) more likely to be symptomatic
- chronic hyponatremia (>24-48 hours) less likely to be symptomatic due to adaptation
 - adaptation: normalization of brain volume through loss of cellular electrolytes (within hours) and organic osmolytes (within days)
 - adaptation is responsible for the risks associated with overly rapid correction
- neurologic symptoms predominate (secondary to cerebral edema) – headache, nausea, malaise, lethargy, weakness, muscle cramps, anorexia, somnolence, disorientation, personality changes, depressed reflexes, decreased level of consciousness (LOC)

Complications

- seizures, coma, respiratory arrest, permanent brain damage, brainstem herniation, death
- risk of brain cell shrinkage with rapid correction of hyponatremia
 - can develop osmotic demyelination of pontine and extrapontine neurons, which may be irreversible (e.g. central pontine myelinolysis: cranial nerve palsies, quadriplegia, decreased LOC)

Risk Factors for Osmotic Demyelination

- rise in serum [Na] with correction >8 mmol/L/d if chronic hyponatremia
- associated hypokalemia and/or malnutrition
- if patient with hyponatremia and hypovolemia is given large volume of isotonic fluid (ADH is stimulated by hypovolemia; when hypovolemia is corrected, the ADH level falls suddenly causing sudden brisk water diuresis, and therefore rapid rise in serum Na level)
- patient with psychogenic polydipsia, deprived of water

Investigations

- ECF volume status assessment
- serum electrolytes, glucose, Cr
- serum osmolality, urine osmolality
- urine Na <10-20 mmol/L suggests volume depletion as the cause of hyponatremia
- assess for causes of SIADH (see Table 5)
- TSH, free T4, and cortisol levels
- consider CT chest if suspect pulmonary cause of SIADH
- consider CT head if suspect CNS cause

Treatment of Hyponatremia

- general measures for all patients
 - water restrict (1 L/day)
 - treat underlying cause
 - monitor serum Na frequently to ensure correction is not occurring too rapidly
 - monitor urine output frequently: high output of dilute urine is the first sign of dangerously rapid correction of hyponatremia

A. Definitely Acute (known to have developed over <24-48 hours)

- commonly occurs in hospital (dilute IV fluid + reason for ADH excess e.g. post-operative)
- less risk from rapid correction since adaptation has not fully occurred
- if symptomatic
 - correct rapidly with 3% NaCl 1-2 cc/kg/h up to serum Na=125-130 mmol/L
 - may need furosemide to address volume overload
- if asymptomatic, treatment depends on severity
 - if marked fall in plasma [Na], treat as symptomatic

B. Chronic or Unknown

1. if severe symptoms (seizures or decreased LOC)
 - must partially correct acutely
 - aim for increase of Na by 1-2 mmol/L/hr for 4-6 hrs
 - limit total rise to 8 mmol/L in 24 hrs
 - IV 3% NaCl at 1-2 cc/kg/hr
 - may need furosemide
2. if asymptomatic
 - water restrict to < 1 L/day fluid intake
 - consider IV 0.9% normal saline (NS) + furosemide (reduces urine osmolality, augments excretion of electrolyte-free H₂O)
 - consider NaCl tablet or Oxocubes® as a source of Na
3. refractory
 - furosemide and IV NS
 - demeclocycline 300-600 mg PO bid (antagonizes effect of ADH on collecting duct; avoid if cirrhosis or congestive heart failure as nephrotoxic in these settings)
 - extra osmoles – give oral urea (increases loss of water without Na; 30-60 g/day)
 - slow rate of IV 3% NaCl (e.g. 10 cc/hr = 120 mmol/day of sodium which will increase serum [Na] by about 3 mmol/L/day)

C. Options if overly rapid correction occurs

- give water (i.e. switch to IV D5W)
- give ADH to stop water diuresis (DDAVP 1-2 µg IV)

Impact of IV Solution on Plasma Na

- formula to estimate the change in serum Na caused by retention of 1 L of any infusate [TBW = (for men) 0.6 x wt(kg); (for women) 0.5 x wt(kg)]

$$\text{change in serum Na} = \frac{\text{infusate [Na]} - \text{serum [Na]}}{\text{TBW} + 1 \text{ L}}$$

- this formula assumes there are no losses of water or electrolytes



Beware of Rapid Correction of Hyponatremia

- Inadvertent rapid correction of hyponatremia can easily occur
 - e.g. patient with hyponatremia due to SIADH from nausea
 - Gravidol® given for relief of hyponatremia induced nausea
 - ADH quickly turned off in the absence of nausea, the kidneys rapidly excrete the excess free water, and the serum [Na⁺] rises rapidly
 - Patient at risk of osmotic demyelination
- High output dilute urine (>100 cc/hr, <100 mOsm/L) in the setting of hyponatremia is usually the first sign of dangerously rapid correction of serum sodium



Correction of Na in hyponatremia should not exceed 8mmol/L/24 hrs unless definitely known to be <24-48 hrs duration. Frequent monitoring of serum Na and urine output is essential.



Concentration of Na in Common Infusates

Na in 0.45% NaCl = 77 mmol/L
 Na in 0.9% NaCl = 154 mmol/L
 Na in 3% NaCl = 513 mmol/L
 Na in 5% NaCl = 855 mmol/L
 Na in Ringer's lactate = 130 mmol/L
 Na in D5W = 0



H₂O Deficit and TBW Equations

1. TBW = 0.6 x wt (kg) men; TBW = 0.5 x wt (kg) women
2. H₂O deficit = TBW x ([Na]plasma – 140) / 140

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

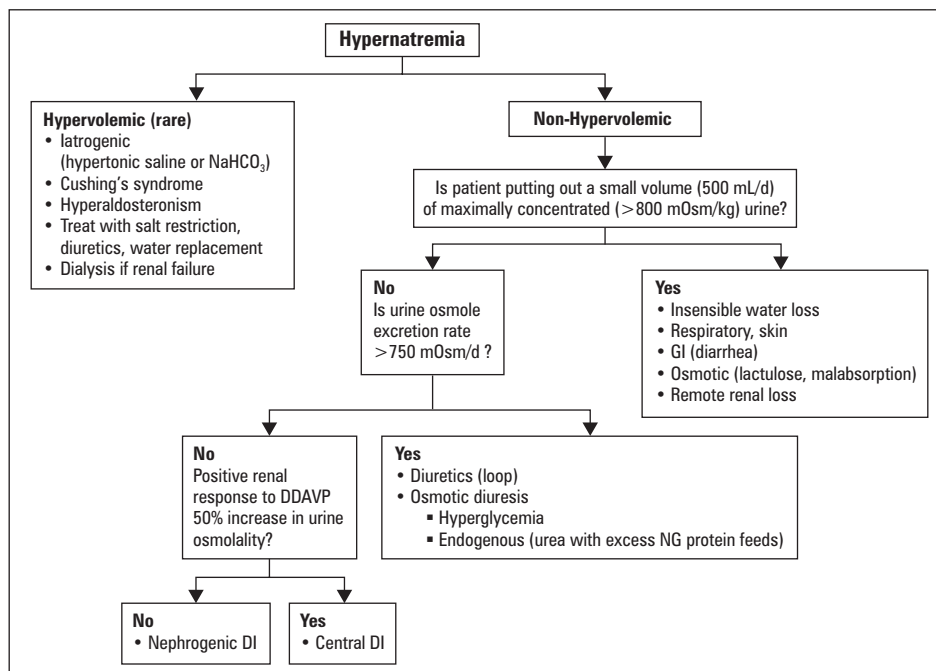
1. urine that is inappropriately concentrated for the serum osmolality
2. high urine sodium (>20 - 40 mmol/L)
3. high FE_{Na}

Table 5. Disorders Associated with SIADH

Tumour	Pulmonary	CNS	Drugs	Miscellaneous
Small cell Ca	Pneumonia	Mass lesion	Antidepressants	Post-op state
Bronchogenic Ca	Lung abscess	Encephalitis	TCAs	Pain
AdenoCa of pancreas	TB	Subarachnoid hemorrhage	SSRIs	Severe nausea
Hodgkin's disease	Acute respiratory failure	Stroke	Antineoplastics	HIV
Thymoma	Positive pressure ventilation	Head trauma	Vincristine	
		Acute psychosis	Cyclophosphamide	
		Acute intermittent porphyria	Other	
			DDAVP	
			Oxytocin	
			Nicotine	
			Carbamazepine	
			Barbiturates	
			Chlorpropamide	

**Hypernatremia**

- hypernatremia: serum $[Na]$ >145 mmol/L
- too little water relative to total body Na; always a hyperosmolar state
- usually due to net water loss, rarely due to hypertonic Na gain
- results from problems with water intake (access, thirst) and/or site of increased water loss (renal or extrarenal)
- less common than hyponatremia because patients are protected against hypernatremia by thirst and release of ADH

**Figure 8. An Approach to Hypernatremia****Signs and Symptoms**

- with acute hypernatremia no time for adaptation, therefore more likely to be symptomatic
- adaptive response: cells import and generate new osmotically active particles to normalize size
- due to brain cell shrinkage: altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, seizures, coma, death
- \pm polyuria, thirst, signs of hypovolemia

Complications

- increased risk of vascular rupture resulting in intracranial hemorrhage
- rapid correction may lead to cerebral edema due to ongoing brain hyperosmolarity

Treatment of Hypovolemic Hypernatremia

- general measures for all patients
 - give free water (oral or IV)
 - treat underlying cause
 - monitor serum Na frequently to ensure correction is not occurring too rapidly
- if evidence of hemodynamic instability, must first correct volume depletion with NS bolus
- loss of water is often accompanied by loss of Na but a proportionately larger water loss
- in patients with presumed normal total body Na content, use formula to calculate water deficit:

$$\text{H}_2\text{O deficit} = \frac{\text{TBW} \times (\text{serum [Na]} - 140)}{140}$$
 [TBW = 0.6 x wt(kg) for men, 0.5 x wt(kg) for women]
- replace free water deficit; “free water” is water without sodium
- encourage patient to drink pure water, as oral route is preferred for fluid administration
- if unable to replace PO or NG, correct H₂O deficit with hypotonic IV solution
 - 1L D5W approximately equals 1 L free water
 - 1L 0.45% NS approximately equals 500 mL free water
- use formula (see *Hyponatremia*, NP11) to estimate expected change in serum Na with 1 L infusate
- aim to to lower [Na] by no more than 12 mmol/L in 24 hours (0.5 mmol/L/hr)
- must also provide maintenance fluids and replace ongoing losses
- rule of thumb: give 2 cc/kg/hour of free water to correct serum [Na] by about 0.5 mmol/L/hour or 12 mmol/L/day



Correction of serum [Na] in hypernatremia should not exceed 12 mmol/L/24 hrs.

Treatment of Hypervolemic Hypernatremia

- general measures as above
- hypervolemic hypernatremia: remove excess total body Na with diuresis or dialysis (if renal failure present), then replace water deficit using D5W

DIABETES INSIPIDUS (DI)

- collecting tubule is impermeable to water due to absence of ADH or impaired response to ADH
- central defect in release of ADH (central DI) or renal response to ADH (nephrogenic DI)

Etiology

- central DI: neurosurgery, granulomatous diseases, trauma, vascular events, and malignancy
- nephrogenic DI: lithium (most common), hypokalemia, hypercalcemia, and congenital

Diagnosis

- urine osmolality inappropriately low in patient with hypernatremia ($U_{\text{osm}} < 300 \text{ mOsm/kg}$)
- serum vasopressin concentration may be absent or low (central), or elevated (nephrogenic)
- dehydration test: H₂O deprivation until loss of 3% of body weight or until urine osmolality rises above plasma osmolality; if fails to concentrate urine, most likely DI
- administer DDAVP (exogenous ADH) (10 µg intranasally or 2 µg SC):
 - central DI: diagnosed if there is rise in urine osmolality, fall in urine volume
 - ♦ treat with DDAVP
 - nephrogenic DI: exogenous ADH fails to concentrate urine as kidneys do not respond
 - ♦ treat with water (IV D5W or PO water), thiazides may help as well (reduced ECF volume stimulates proximal tubular reabsorption of sodium and water, leading to less delivery of glomerular filtrate to ADH sensitive parts of renal tubule, and therefore lower urine volume results)

Potassium Homeostasis

- approximately 98% of total body K stores are intracellular
- normal serum K ranges from 3.5-5.0 mEq/L
- in response to K load, rapid removal from ECF is necessary to prevent life-threatening hyperkalemia
- insulin, catecholamines and acid-base status influence K movement into cells
 - aldosterone has a minor effect
- potassium excretion is regulated at the distal nephron
 - $\text{K excretion} = \text{urine flow rate} \times \text{urine [K]}$

Factors which Increase Renal K Loss

- hyperkalemia
- increased distal tubular urine flow rate and Na delivery (thiazides and loop diuretics)
- increased aldosterone activates epithelial sodium channel (eNaC) in cortical collecting duct, causing Na reabsorption and K excretion
- metabolic alkalosis
- hypomagnesemia
- increased non-reabsorbable anions in tubule lumen: HCO₃, penicillin, salicylate



Hypokalemia

- serum $[K] < 3.5$ mEq/L

Approach to Hypokalemia

- emergency measures: obtain ECG; if potentially life threatening, begin treatment immediately
- rule out transcellular shifts of K as cause of hypokalemia
- assess contribution of dietary K intake
- 24-hr K excretion or spot urine K
- TTKG = transtubular potassium gradient = $(U_k/P_k)/(U_{osm}/P_{osm})$
- if renal K loss, check BP and acid-base status
- may also assess plasma renin and aldosterone levels, serum $[Mg]$

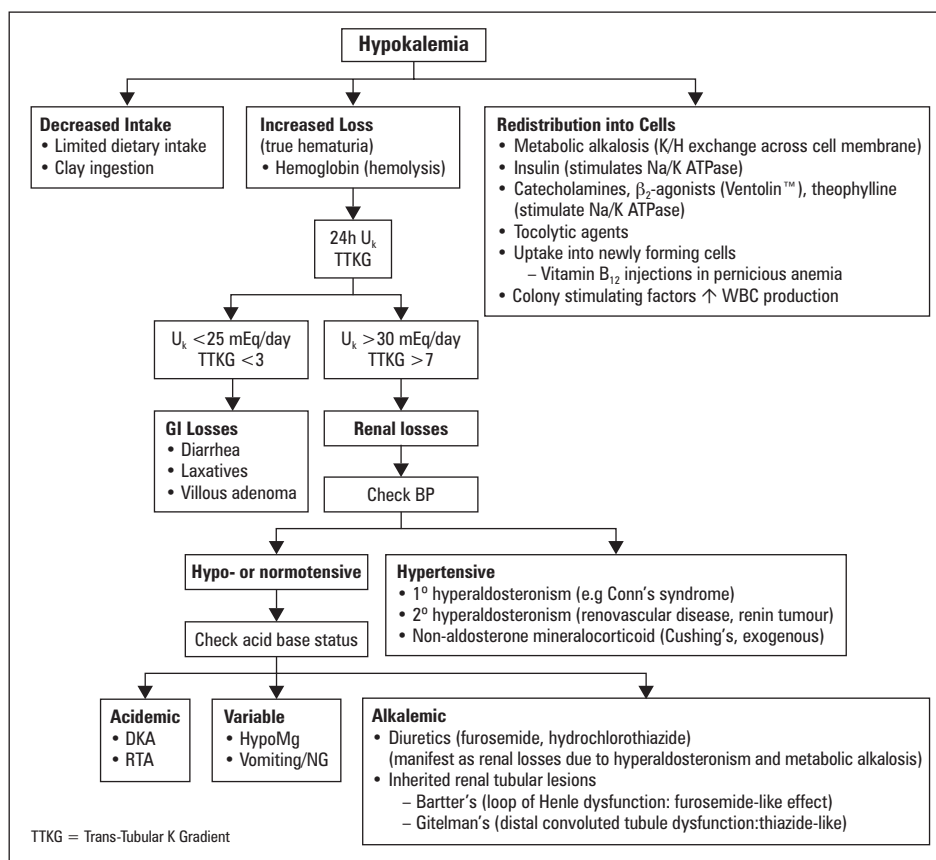


Figure 9. An Approach to Hypokalemia

Signs and Symptoms

- usually asymptomatic, particularly when mild (3.0-3.5 mmol/L)
- nausea, vomiting, fatigue, generalized weakness, myalgia, muscle cramps, and constipation
- if severe: arrhythmias, muscle necrosis, and rarely paralysis with eventual respiratory impairment
- arrhythmias occur at variable levels of K; more likely if digoxin use, hypomagnesemia, or CAD
- ECG changes are more predictive of clinical picture than serum $[K]$
 - U waves most important (low amplitude wave following a T wave)
 - flattened or inverted T waves
 - depressed ST segment
 - prolongation of Q-T interval
 - with severe hypokalemia: P-R prolongation, wide QRS, arrhythmias; increases risk of digitalis toxicity

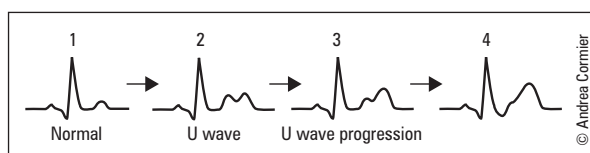


Figure 10. ECG Changes in Hypokalemia

Treatment

- treat underlying cause
- if urine output and renal function are impaired, correct with extreme caution
- risk of hyperkalemia with potassium replacement especially high in elderly, diabetics, and patients with decreased renal function
- beware of excessive potassium repletion, especially if transcellular shift caused hypokalemia
- if true K deficit, potassium repletion (decrease in serum [K] of 1 mEq is very roughly 100-200 mEq of total body loss)
 - oral sources – food, tablets (K-Dur®), KCl liquid solutions
 - IV – usually KCl in saline solutions, avoid dextrose solutions (may exacerbate hypokalemia via insulin release)
 - max. 40 mmol/L via peripheral vein, 60 mmol/L via central vein, max. infusion 20 mmol/hr
- K-sparing diuretics (triamterene, spironolactone, amiloride) can prevent renal K loss
- restore Mg if necessary

Hyperkalemia



- serum [K] >5.0 mEq/L

Approach to Hyperkalemia

1. emergency measures: obtain ECG, if life threatening begin treatment immediately
2. rule out factitious hyperkalemia; repeat blood test
3. hold exogenous K, and any K retaining medications
4. assess potential causes of transcellular shift
5. estimate GFR (calculate CrCl using Cockcroft-Gault)
6. if normal GFR, calculate TTKG = $(U_k/P_k)/(U_{osm}/P_{osm})$
 - TTKG <7 = decreased effective aldosterone function
 - TTKG >7 = normal aldosterone function

Table 6. Causes of Hyperkalemia

Factitious	Increased Intake	Cellular Release	Decreased Excretion
Sample hemolysis*	Diet	Intravascular hemolysis	Decreased GFR
Sample taken from vein where IV KCl is running	KCl tabs	Rhabdomyolysis	• Renal failure
Prolonged use of tourniquet	IV KCl	Insulin deficiency	• Low effective circulating volume
Leukocytosis (extreme)	Salt substitute	Hyperosmolar states (e.g. hyperglycemia)	• NSAIDs in renal insufficiency
Thrombocytosis (extreme)		Metabolic acidosis (except for keto-and lactic acidosis)	Normal GFR but hypoaldosteronism (see Table 7)
		Tumour lysis syndrome	
		Drugs	
		• Beta-blockers	
		• Digitalis overdose (blocks Na/K ATPase)	
		• Succinylcholine	

*Most common

Table 7. Causes of Hyperkalemia with normal GFR

Decreased Aldosterone Stimulus (low renin, low aldosterone)	Decreased Aldosterone Production (normal renin, low aldosterone)	Aldosterone Resistance (decreased tubular response)
Hyporeninemic, hypoaldosteronism	• Adrenal insufficiency of any cause (e.g. Addison's disease, AIDS, metastatic cancer)	K-sparing diuretics
• Associated with DM2, NSAIDs, chronic interstitial nephritis, HIV	• ACE inhibitors	• Spironolactone
	• Angiotensin II receptor blockers	• Amiloride
	• Heparin	• Triamterene
	• Congenital adrenal hyperplasia with 21-hydroxylase deficiency	Other K-sparing drugs
		• Pentamidine
		• Trimethoprim
		• Cyclosporine, tacrolimus
		• Pseudohypoaldosteronism (rare inherited tubular disorders)

Signs and Symptoms

- usually asymptomatic but may develop nausea, palpitations, muscle weakness, muscle stiffness, paresthesias, areflexia, ascending paralysis, and hypoventilation
- impaired renal ammoniogenesis and metabolic acidosis
- ECG changes and cardiotoxicity (do not correlate well with serum [K])
 - peaked and narrow T waves
 - decreased amplitude and eventual loss of P waves
 - prolonged PR interval

- widening of QRS and eventual merging with T wave (sine-wave pattern)
- AV block
- ventricular fibrillation, asystole



In patients with diabetes and increased $[K^+]$ and hyperglycemia, often just giving insulin to restore euglycemia is sufficient to correct the hyperkalemia.

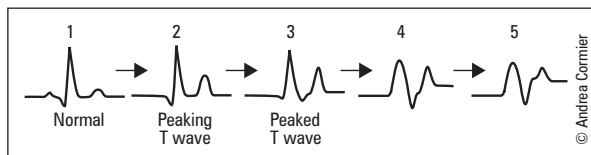


Figure 11. ECG Changes in Hyperkalemia

Treatment

- acute therapy is warranted if ECG changes are present, or if patient is symptomatic
- tailor therapy to severity of increase in $[K]$ and ECG changes
 - $[K] < 6.5$ and normal ECG
 - ♦ treat underlying cause, stop K intake, increase the loss of K via urine and/or GI tract (see below)
 - $[K]$ between 6.5 and 7.0, no ECG changes: add insulin to above regimen
 - $[K] > 7.0$ and/or ECG changes: first priority is to protect the heart, add Ca gluconate to above

1. Protect the Heart

- Ca gluconate 1-2 amps (10 mL of 10% solution) IV
- antagonizes cardiac toxicity of hyperkalemia, protects cardiac conduction system, no effect on serum $[K]$
- onset within minutes, lasts 30-60 minutes

2. Shift K into Cells

- regular insulin (Insulin R) 10-20 units IV, with 1-2 amp D50W (give D50W before insulin)
 - onset of action 15-30 min, lasts 1-2 h
 - monitor capillary blood glucose q1h because of risk of hypoglycemia
 - can repeat every 4-6 hours
- $NaHCO_3$ 1-3 amps (given as 3 amps of 7.5% or 8.4% $NaHCO_3$ in 1L D5W)
 - onset of action 15-30 min, transient effect, drives K into cells in exchange for H
- β_2 -agonist (Ventolin®) in nebulized form (dose = 2 cc or 10 mg inhaled) or 0.5 mg IV
 - onset of action 30-90 min, stimulates Na/K ATPase
 - caution if patient has heart disease as tachycardia may result from this high dose of β_2 -agonist

3. Enhance K Removal from Body

- via urine (preferred approach)
 - furosemide (≥ 40 mg IV), may need IV NS to avoid hypovolemia
 - fludrocortisone (synthetic mineralocorticoid) if suspect aldosterone deficiency
- via gastrointestinal tract
 - cation-exchange resins: calcium resonium or Kayexalate® (increasingly falling out of favor as they bind Na in exchange for K, and controversial how much K is actually removed – main benefit may be the diarrhea it causes) plus sorbitol PO to avoid constipation (must ensure that patient has a bowel movement after resin is administered)
 - Kayexalate® enemas with tap water (not sorbitol enemas as they can cause colonic necrosis)
- dialysis (renal failure, life threatening hyperkalemia unresponsive to therapy)

Acid-Base Disorders

- acid-base homeostasis influences protein function and can critically affect tissue and organ function with consequences to cardiovascular, respiratory, metabolic and CNS function
- see Respirology, R5 for more information on respiratory acidosis/alkalosis
- normal concentration of $HCO_3^- = 24$ mEq/L
- normal $pCO_2 = 40$ mmHg
- each acid base disorder has an appropriate compensation
 - inadequate compensation or overcompensation indicates the presence of a second acid-base disorder
 - e.g. in metabolic acidosis, inadequate compensation means there is also respiratory acidosis; overcompensation means there is also respiratory alkalosis



Treatment of Hyperkalemia

SEE BIG K DROP

SEE – Calcium gluconate

BIG – β -agonist, Bicarb, Insulin, Glucose

K – Kayexalate®

DROP – Diuretics, Dialysis

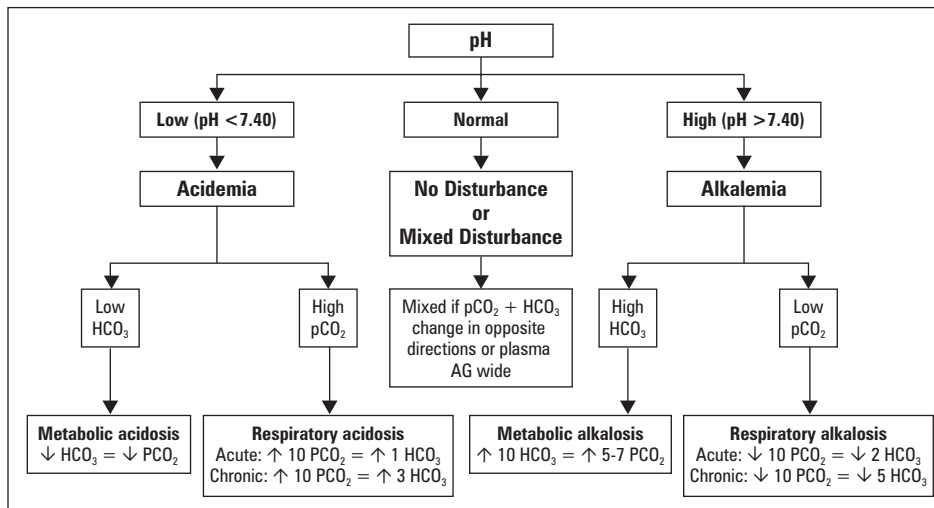


Figure 12. An Approach to Acid-Base Disorders

Metabolic Acidosis

Identify Main Disturbance, then:

1. Evaluate compensation (Figure 12)
2. Calculate plasma anion gap (PAG)
 - $\text{PAG} = \text{Na} - (\text{HCO}_3 + \text{Cl})$ baseline = 12, range 10-14
 - PAG can be altered by plasma albumin level: for each 10 g/L fall in albumin, lower baseline PAG by 3 (e.g. if plasma [albumin] = 20 g/L, expect PAG = 6)
3. If PAG elevated, compare increase in PAG with decrease in HCO_3
 - if increase in PAG < decrease in HCO_3 , there is a coexisting non-AG metabolic acidosis
 - if increase in PAG > decrease HCO_3 , there is a coexisting metabolic alkalosis
4. Calculate osmolar gap
 - osmolar gap = measured osmolality – calculated osmolality
 - ♦ calculated osmolality = $(2 \times \text{Na}) + \text{urea} + \text{glucose}$ (all units are in mmol/L)
 - ♦ normal osmolar gap < 10
 - ♦ if gap > 10, consider: methanol poisoning, ethylene glycol poisoning, OR another cause of acidosis plus ethanol ingestion

Etiology and Pathophysiology

1. Increased PAG Metabolic Acidosis (4 types)

1. Lactic acidosis (2 types)
 - ♦ L-lactic acid
 - Type A: due to tissue hypoperfusion (any cause of shock), ischemic bowel, profound hypoxemia
 - Type B: failure to metabolize normally produced lactic acid in the liver due to severe liver disease, excessive alcohol intake, thiamine deficiency, or metformin accumulation (metformin interferes with electron transport chain)
 - ♦ D-lactic acid: rare syndrome characterized by episodes of encephalopathy and metabolic acidosis, requires carbohydrate malabsorption (e.g. short bowel syndrome), colonic bacteria that produce D-lactic acid, a carbohydrate load, diminished colonic motility and impaired D-lactate metabolism
2. Ketoacidosis
 - ♦ diabetic
 - ♦ starvation
 - ♦ alcoholic (decreased carbohydrate intake and vomiting)
3. Toxins
 - ♦ methanol (toxic to brain and retina, can cause blindness and brain death) – metabolized to formic acid
 - ♦ ethylene glycol (toxic to brain and kidneys) – metabolized to oxalic acid (envelope shaped crystals in urine)
 - ♦ salicylate
4. Advanced renal failure (i.e. serum Cr increased at least 5x above baseline – a very low GFR causes anion retention, and renal disease leads to impaired bicarbonate production)



Useful Equations

1. $\text{PAG} = [\text{Na}] - [\text{Cl}] - [\text{HCO}_3^-]$ (normal range = 10-14)
2. Osmolar Gap = measured osmolality – calculated osmolality (normal < 10)
3. Calculated Osmolality = $2[\text{Na}] + [\text{Urea}] + [\text{Glucose}]$



Causes of Increased Anion Gap Metabolic Acidosis

MUDDPILES

Methanol
Uremia
Diabetic/alcoholic/starvation ketoacidosis
Paraldehyde
Isopropyl alcohol/iron
Lactic acidosis
Ethylene glycol
Salicylates

or

KARMEL

Ketoacidosis
ASA
Renal Failure
Methanol
Ethylene Glycol
Lactic Acidosis



Causes of Non-Anion Gap Metabolic Acidosis

HARDUP

Hyperalimentation
Acetazolamide
RTA*
Diarrhea*
Ureteroenteric fistula
Pancreaticoduodenal fistula increased
*Most Common



3 Clinical Scenarios that Produce a Mixed Disorder with Near Normal pH

(i.e. increased PAG metabolic acidosis + resp. alkalosis)

- Cirrhosis
- ASA overdose
- Sepsis

2. Normal PAG Metabolic Acidosis (Hyperchloremic Acidosis)

- diarrhea (HCO_3^- loss from GI tract)
- RTA (renal tubular acidosis)
 - ♦ type I RTA (distal): inability to fully excrete H^+ load as NH_4^+ , therefore accumulates
 - ♦ type II RTA (proximal): impaired HCO_3^- reabsorption
 - ♦ type IV RTA: defective ammoniogenesis due to decreased aldosterone, hyposponsiveness or hyperkalemia
- to help distinguish renal causes from non-renal causes, use Urine Anion Gap = $(\text{Na} + \text{K}) - \text{Cl}$
- calculation establishes the presence or absence of unmeasured +ve ions (e.g. NH_4^+) in urine
 - if <0 , suggests adequate NH_4^+ in urine (likely nonrenal cause: diarrhea)
 - if >0 , suggests problem is lack of NH_4^+ in urine (e.g. distal RTA)

Treatment of Metabolic Acidosis

- treat underlying cause
 - insulin for DKA
 - restore tissue perfusion for Type A lactic acidosis
 - ethanol + dialysis for methanol or ethylene glycol poisoning
 - alkaline diuresis ± dialysis if ASA overdose
- correct coexisting disorders of K (see *Hyperkalemia*, NP15)
- consider treatment with exogenous alkali (e.g. NaHCO_3) if:
 - severe reduction in $[\text{HCO}_3^-]$ e.g. <8 mmol/L, especially with very low pH (<7)
 - no metabolizable anion (e.g. salicylate, formate, oxalate, sulphate)
- note: lactate and ketoacid anions can be metabolized to HCO_3^-
- risks of sodium bicarbonate therapy
 - hypokalemia: causes K to shift into cells (correct K deficit first)
 - ECF volume overload: Na load given with NaHCO_3 , can exacerbate pulmonary edema
 - overshoot alkalosis: abrupt, poorly tolerated transition from overly aggressive alkali loading, partial conversion of accumulated organic anions to HCO_3^- and persisting hyperventilation

Metabolic Alkalosis

Pathophysiology

- requires initiating event and maintenance factors
- initiating event
 - GI (vomiting, NG tube) or renal loss of H^+
 - exogenous alkali (oral or parenteral administration), milk alkali syndrome
 - diuretics (contraction alkalosis): decreased excretion of HCO_3^- , decreased ECF volume, therefore increased $[\text{HCO}_3^-]$
 - post-hypercapnia: renal compensation for respiratory acidosis is HCO_3^- retention, rapid correction of respiratory disorder results in transient excess of HCO_3^-
- maintenance factors
 - volume depletion: increased proximal reabsorption of NaHCO_3 and increased aldosterone
 - hyperaldosteronism (1° or 2°): distal Na reabsorption in exchange for K and H excretion leads to HCO_3^- generation, aldosterone also promotes hypokalemia
 - hypokalemia: transcellular K/H exchange, stimulus for ammoniogenesis and HCO_3^- generation

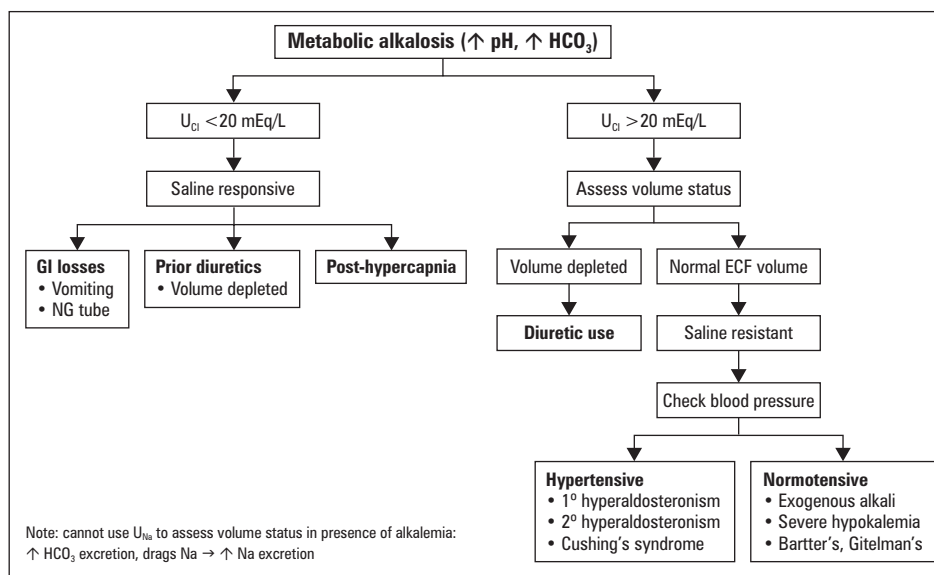


Figure 13. An Approach to Metabolic Alkalosis

Evaluate compensation (identify co-existing respiratory acid-base disorders)

- hypoventilation (an upper limit to compensation exists – breathing cannot be stopped; see Figure 12)

Treatment

- treat underlying cause
- correct underlying disease, replenish K and Mg deficits, and possibly K-sparing diuretic
- saline sensitive metabolic alkalosis (most common)
 - treatment: volume repletion
 - \pm carbonic anhydrase inhibitor (e.g. acetazolamide) to facilitate loss of HCO_3^- in urine
- saline resistant metabolic alkalosis
 - ECF volume normal or high
 - usually aldosterone or glucocorticoid excess
 - remove source of aldosterone or glucocorticoid \pm spironolactone

Renal Failure

Presentation of Renal Failure

- signs and symptoms depend on acuity of onset, severity of insult, adaptation to nephron loss/dysfunction, treatment of reversible disease process

1. Volume Overload

- due to increase in total body Na content
- signs: weight gain, HTN, pulmonary or peripheral edema

2. Electrolyte Abnormalities

- high
 - K (decreased renal excretion, increased tissue breakdown)
 - PO_4 (decreased renal excretion, increased tissue breakdown)
 - Ca (rare; happens during recovery phase after rhabdomyolysis-induced acute kidney injury or in settings where hypercalcemia contributes to renal failure, such as in multiple myeloma or sarcoidosis)
 - uric acid
- low
 - Na (failure to excrete excessive water intake)
 - Ca (decreased Vit D activation, hyperphosphatemia, hypoalbuminemia)
 - HCO_3^- (especially with sepsis or severe heart failure)

3. Uremic Syndrome

- retention of urea and other metabolites as well as deficiencies of hormones, causing the manifestations of uremic syndrome

Signs and Symptoms of Renal Failure

- CNS: headache, lethargy, somnolence, confusion, asterixis, hyporeflexia
- PNS: “glove and stocking” type sensory neuropathy, wrist or foot drop
- CVS: shortness of breath, pleuritic chest pain, pericardial friction rub
- GI: anorexia, nausea and vomiting, decreased taste
- GU: irritative and/or obstructive urinary tract symptoms (e.g. frequency, urgency, straining, nocturia), hematuria, palpable bladder (if bladder problem has contributed to renal failure)
- endocrine: weight loss, amenorrhea, decreased libido
- MSK: nocturnal muscle cramps, muscle weakness
- skin: pruritus, pallor, yellow discolouration

Complications

- CNS: decreased LOC, stupor, seizure
- CVS: cardiomyopathy, CHF, arrhythmia, pericarditis, atherosclerosis
- GI: peptic ulcer disease, gastroduodenitis, AVM
- hematologic: anemia, bleeding tendency (platelet dysfunction), infections
- endocrine:
 - decreased testosterone, estrogen, progesterone
 - increased FSH, LH
- metabolic:
 - renal osteodystrophy: secondary increased PTH due to decreased Ca, high PO_4 and low active vitamin D
 - ◆ osteitis fibrosa cystica
 - hypertriglyceridemia, accelerated atherogenesis
 - decreased insulin requirements, increased insulin resistance
- dermatologic: pruritus, ecchymosis, hematoma, calciphylaxis (vascular Ca deposition)



The 2 most common causes of acute kidney injury in hospitalized patients are prerenal azotemia and acute tubular necrosis. Remember that prerenal failure can lead to ATN.



Clues to Pre-Renal Etiology

- Clinical: Decreased BP, increased HR, and orthostatic HR and BP changes
- Increased [urea] >> Increased [Cr]
- Urine [Na] <10-20 mmol/L
- Urine osmolality >500 mOsm/kg
- Fractional excretion of Na <1%

Clues to Renal Etiology

- Appropriate clinical context
- Urinalysis positive for casts:
 - Pigmented granular – ATN
 - WBC – AIN
 - RBC – GN

Clues to Post-Renal Etiology

- Known solitary kidney
- Older man
- Recent retroperitoneal surgery
- Anuria
- Palpable bladder
- Ultrasound shows hydronephrosis



Differentiating Pre-renal from ATN

	Pre-renal	ATN
Urinalysis	Normal	RBC, pigmented granular casts
Urine [Na]	<20	>40 mEq/L
Urine [Cr]/[Na]	>40	<20
Urine osmolality	>500	<350 mOsm/kgH ₂ O
FeNa	<1	>1%

Acute Kidney Injury (AKI)

Definition

- abrupt decline in renal function leading to increased nitrogenous waste products
- formerly known as Acute Renal Failure (ARF)

Clinical Features

- azotemia (increased BUN, Cr)
- abnormal urine volume (anuria, oliguria, polyuria)

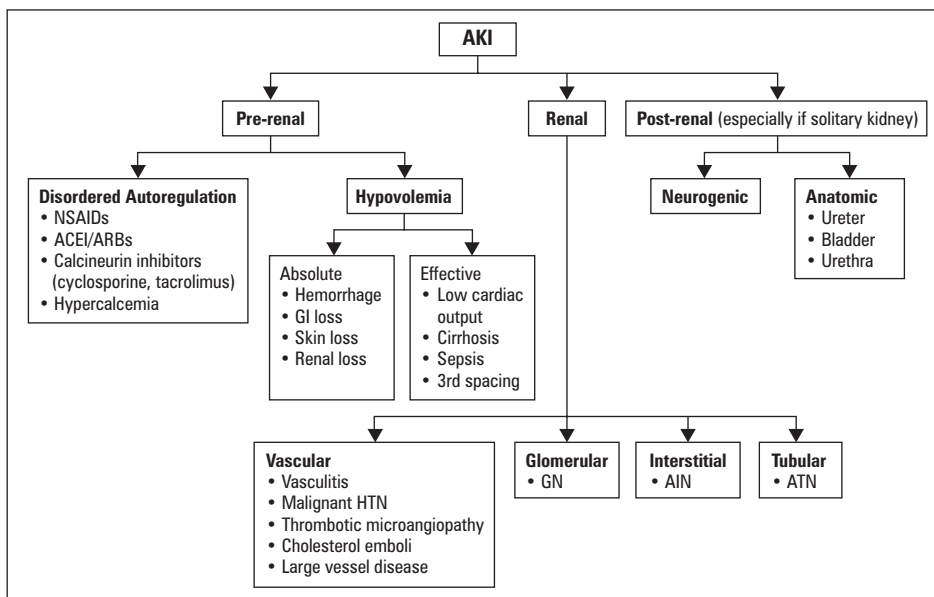


Figure 14. An Approach to Acute Kidney Injury

Approach to AKI

Investigations

- blood: CBC, electrolytes, Cr, urea (think prerenal if increase in urea is relatively greater than increase in Cr), Ca, PO₄
- urine volume, C&S, R&M: sediment, casts, crystals
- urinary indices
- Foley catheterization (rule out bladder outlet obstruction)
- fluid challenge (i.e. fluid bolus to rule out most pre-renal causes)
- imaging: abdo U/S (assess kidney size, hydronephrosis, post-renal obstruction)
- indications for renal biopsy
 - diagnosis is not certain
 - prerenal azotemia or ATN is unlikely
 - oliguria persists >4 weeks

Treatment

- preliminary measures
 - pre-renal
 - correct prerenal factors: optimize volume status and cardiac performance, hold ACEI/ARB
 - renal
 - exclude reversible renal causes: d/c nephrotoxic drugs, treat infection, and optimize electrolytes
 - post-renal
 - consider obstruction: structural (stones, strictures) vs. functional (neuropathy)
 - treat with Foley catheter, indwelling bladder catheter, nephrostomy, stenting
- treat complications
 - fluid overload
 - NaCl restriction
 - high dose loop diuretics
 - hyperkalemia (refer to *Treatment of Hyperkalemia*, NP16)
 - adjust dosages of medications cleared by kidney
- definitive therapy depends on etiology
 - note:** renal transplant is not a therapy for AKI

Prognosis

- high morbidity and mortality in patients with sustained AKI and multi-organ failure

Chronic Kidney Disease (CKD)

Definition

- abnormal markers (Cr, urea)
 - GFR <60 mL/min for >3 months or
 - kidney pathology seen on biopsy or
 - decreased renal size on U/S (kidneys <9 cm)
- clinical features of chronic kidney disease
 - volume overload and hypertension
 - electrolyte and acid-base balance disorders (e.g. metabolic acidosis)
 - uremia

Table 8. Stages of Chronic Kidney Disease (K/DOQI, 2002)

	Definition	GFR (mL/min/1.73m ²)
Stage 1	Normal or increased GFR	≥90
Stage 2	Mild decrease in GFR	60-89
Stage 3a	Moderate decrease in GFR	45-59
Stage 3b	Moderate decrease in GFR	30-44
Stage 4	Severe decrease in GFR	15-29
Stage 5	End stage renal disease	<15 (or dialysis)

Management of Chronic Kidney Disease

- diet
 - protein restriction with adequate caloric intake limits endogenous protein catabolism
 - K restriction (40 mmol/day)
 - Na and water restriction
 - PO₄ restriction (1 g/d)
 - avoid extra-dietary Mg (i.e. antacids)
- medical
 - treatment of secondary hyperparathyroidism
 - calcium supplements (e.g. TUMS®) treats hypocalcemia when given between meals and binds phosphate when given with meals
 - consider calcitriol (1,25-dihydroxy-vitamin D) if hypocalcemic
 - sevelamer (phosphate binder) if both hypercalcemic and hyperphosphatemic
 - vitamin D analogues are being introduced in the near future
 - cinacalcet for hyperparathyroidism (sensitizes parathyroid to Ca, decreasing PTH)
 - sodium bicarbonate for metabolic acidosis
 - erythropoietin injections (Hct <30%) for anemia; target Hct 33-36%
 - DDAVP for prolonged bleeding time if patient has clinical bleeding or invasive procedures
 - ACEI for hypertension (target 130/80 or less), loop diuretics when GFR <25 mL/min
 - statins for dyslipidemia
 - adjust dosages for renally excreted medications (avoid nephrotoxic medications)
- dialysis (hemodialysis, peritoneal dialysis)
- renal transplantation


Incidence of Etiologies of Chronic Kidney Disease (CKD)

Diabetes	42.9%
Hypertension	26.4%
Glomerulonephritis	9.9%
Other/Unknown	7.7%
Interstitial nephritis/	
Pyelonephritis	4.0%
Cystic/Hereditary/Congenital	3.1%
Secondary GN/Vasculitis	2.4%


Management of Complications of CKD
NEPHRON

- N** – Low-nitrogen diet
- E** – Electrolytes: monitor K
- P** – pH: metabolic acidosis
- H** – Hypertension
- R** – RBCs: manage anemia with erythropoietin
- O** – Osteodystrophy: give calcium between meals (to increase Ca) and calcium with meals (to bind and decrease PO₄)
- N** – Nephrotoxins: avoid nephrotoxic drugs (ASA, gentamicin) and adjust doses of renally excreted medications

Renin Angiotensin System Blockade and Cardiovascular Outcomes in Patients with Chronic Kidney Disease and Proteinuria: A Meta-analysis

Am Heart J 2008; 155:791-805

Purpose: To evaluate the role of renin angiotensin system (RAS) blockade in improving cardiovascular CV outcomes in patients with chronic kidney disease.

Study Selection: Randomized controlled trials that analyzed CV outcomes in patients with chronic kidney disease (CKD)/proteinuria treated with RAS blockade (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers). Renin angiotensin system blockade-based therapy was compared with placebo and control (beta-blocker, calcium-channel blockers and other antihypertensive-based therapy) therapy in the study.

Results: Twenty-five trials (N = 45758) were included. Compared to placebo, RAS blockade reduced the risk of heart failure in patients with diabetic nephropathy. In patients with non-diabetic CKD, RAS blockade decreased CV outcome compared to control therapy.

Conclusions: RAS blockade reduced CV outcomes in diabetic nephropathy as well as non-diabetic CKD.

Renal Replacement Therapy

Dialysis



Indications for Dialysis

Hyperkalemia (refractory)
 Acidosis (refractory)
 Volume overload (refractory)
 Elevated urea (>35-50 mM)
 Pericarditis
 Encephalopathy
 Edema (pulmonary)

or

Acidosis (refractory)
 Electrolyte imbalance (refractory)
 ▪ Hyperkalemia
 Intoxication (e.g. methanol)
 Overload (refractory volume overload)
 ▪ Pulmonary edema
 Uremia
 ▪ Encephalopathy, pericarditis, urea >35-50 mM



How to Write Dialysis Orders (MUST BE INDIVIDUALIZED)

- Filter Type (e.g. F80)
- Length (e.g. 4h 3 times/wk or 2h daily)
- Q Blood Flow (Max 400 cc/min)
- Ultrafiltration (e.g. 2L or to target dry weight)
- Na 140 (can be adjusted by starting at 155 and "ramping" down to minimize cramping)
- K (based on serum [K])

Serum K	Dialysate
4-6	1.5
3.5-4	2.5
<3.5	3.5
- Ca 1.25
- HCO₃ 40
- Heparin (none, tight [500 U/h] or full [1000 U/h])
- IV fluid to support BP (e.g. N/S)



When to Initiate DIALYSIS

- CrCl <20 mL/min
- Educate patient regarding dialysis; if not a candidate for peritoneal dialysis, make arrangements for AV fistula
- CrCl <15 mL/min
- Weigh risk and benefits for initiating dialysis
- CrCl <10 mL/min
- Dialysis should be initiated

NOTE

- Cockcroft-Gault equation (or Modification of Diet in Renal Disease equation) should be used to measure kidney function
- Monitor for uremic complications
- Significant benefits in quality of life can occur if dialysis started before CrCl <15 mL/min
- It is unclear whether patients who start dialysis early have increased survival
- A preemptive transplant can be considered if patient is stable, in order to avoid dialysis

From: National Kidney Foundation/Kidney Disease Outcome. Quality Initiative

Indications for Dialysis in Chronic Renal Failure

- absolute indications
 - volume overload unresponsive to medication
 - hyperkalemia unresponsive to medication
 - severe metabolic acidosis unresponsive to medication
 - neurologic signs or symptoms of uremia (encephalopathy, neuropathy, seizures)
 - uremic pericarditis
 - refractory accelerated hypertension
 - clinically significant bleeding diathesis
 - persistent severe nausea and vomiting
 - plasma Cr >1060 µmol/L (12 mg/dL) or BUN >36 mmol/L (100 mg/dL; clinical picture also important)
- relative indications
 - anorexia
 - decreased cognitive functioning
 - profound fatigue and weakness
 - severe anemia unresponsive to erythropoietin
 - persistent severe pruritus
 - restless leg syndrome
- **hemodialysis:** blood is filtered across a semipermeable membrane removing accumulated toxic waste products, solutes, excess fluid (ultrafiltration), and restoring buffering agents to the bloodstream
 - available as intermittent (e.g. three times per week), continuous (CVVHD) or sustained low efficiency (SLED)
- **peritoneal dialysis:** peritoneum acts as a semipermeable membrane similar to hemodialysis filter
 - advantages: independence, fewer stringent dietary restrictions, better rehabilitation rates
 - available as continuous ambulatory (CAPD; four exchanges per day) or cyclic (CCPD; machine carries out exchanges overnight)
- patients with chronic kidney disease should be referred for surgery to attempt construction of a primary AV fistula when their eGFR is <20 mL/min, the serum Cr level quoted as >350 µmol/L (>4.0 mg/dL), or within 1 year of an anticipated need
- refer patients with chronic renal disease to a nephrologist early on to facilitate treatment and plan in advance for RRT

Table 9. Peritoneal Dialysis vs. Hemodialysis

	Peritoneal Dialysis	Hemodialysis
Rate	Slow	Fast
Location	Home	Hospital (usually)
Ultrafiltration	Osmotic pressure via dextrose dialysate	Hydrostatic pressure
Solute Removal	Concentration gradient and convection	Concentration gradient and convection
Membrane	Peritoneum	Semi-permeable artificial membrane
Method	Indwelling catheter in peritoneal cavity	Line from vessel to artificial kidney
Complications	Infection at catheter site Bacterial peritonitis Metabolic effects of glucose Difficult to achieve adequate clearance in patients with large body mass	Vascular access (clots, collapse) Bacteremia Bleeding due to heparin Hemodynamic stress of extracorporeal circuit Disequilibrium syndrome (headache, cerebral edema, hypotension, nausea, muscle cramps related to solute/water flux over short time)
Preferred When	Young, high functioning, residual renal function Success depends on presence of residual renal function	Bed-bound, co-morbidities, no renal function Residual renal function not as important

Renal Transplantation

- preferred modality of RRT, best way to reverse uremic signs and symptoms
- provides maximum replacement of GFR
- only therapy shown to improve survival in patients with ESRD
- native kidneys usually left in situ
- 2 types: deceased donor, living donor (related or unrelated)
- kidney transplanted into iliac fossa, transplant renal artery anastomosed to external iliac artery of recipient
- 1 year renal allograft survival rates $\geq 90\%$

Complications

- leading causes of late allograft loss: chronic rejection and death with functioning graft
- #1 cause of mortality in transplanted patients is cardiovascular disease
- immunosuppressant drug therapy: side effects include infections, malignancy (skin, Kaposi's sarcoma, post-transplant lymphoproliferative disorder)
- acute rejection: graft site tenderness, rise in Cr, oliguria, \pm fever
- de novo glomerulonephritis (usually membranous)
- new-onset diabetes mellitus (often due to prednisone use)
- cyclosporine or tacrolimus nephropathy (refer to *Small Vessel Disease*, NP32)
- chronic allograft nephropathy
 - early allograft damage caused by episodes of acute rejection and acute peritransplant injuries
 - immunologic and nonimmunologic factors (HTN, hyperlipidemia, age of donor, quality of graft, new onset diabetes)
- CMV (cytomegalovirus) infection and other opportunistic infections usually occur between 1 and 6 months post-transplant
- BK virus (polyoma virus) nephropathy can result from over-immunosuppression and lead to graft loss

Glomerular Disease

Terminology of Glomerular Changes

- terms applying to a population of glomeruli in the kidney
 - diffuse: majority of glomeruli abnormal ($>50\%$)
 - focal: some glomeruli affected
- terms applying to an individual glomerulus
 - global: entire glomerulus abnormal
 - segmental: only part of the glomerulus abnormal

Types of Changes

- proliferation: hyperplasia of one of the glomerular cell types (mesangial, endothelial, parietal epithelial), with or without inflammatory cell infiltration
- membranous changes: capillary wall thickening due to immune deposits or alterations in basement membrane
- crescent formation: parietal epithelial cell proliferation and mononuclear cell infiltration from crescent-shape in Bowman's space

Presentation of Glomerular Disease

Important Points To Remember

- each glomerulopathy presents as one of 4 major glomerular syndromes
 - acute nephritic
 - nephrotic
 - rapidly progressive glomerulonephritis
 - asymptomatic urinary abnormalities
- each glomerulopathy can be caused by a primary disease OR can occur secondary to a systemic disease
- some glomerulopathy can present as more than one syndrome at different times

1. ACUTE NEPHRITIC SYNDROME

Clinical/Lab Features

- proteinuria (but <3.5 g/1.73 m²/day)
- abrupt onset hematuria (microscopic or macroscopic)
- azotemia (increased Cr and urea)



Commonly Used Immunosuppressive Drugs

Calcineurin inhibitors

- Cyclosporine
- Tacrolimus

Antiproliferative medications

- Mycophenolate Mofetil
- Azathioprine

Other agents

- Sirolimus
- Prednisone

Anti-lymphocyte antibodies

- Thymoglobulin
- Basiliximab

Survival Among Nocturnal Home Haemodialysis Patients Compared to Kidney Transplant Recipients

Nephrol Dial Transplant 2009; 24:2915-2919

Study: Retrospective, matched cohort with 4-5 years average follow up

Population: 177 nocturnal home dialysis (NHD) patients (mean age 46, 68% white) were matched to 533 deceased donor transplant (DTX) patients and 533 live donor (LTX) transplant patients (1:3:3 ratio)

Intervention: Nocturnal home dialysis versus live or deceased donor transplant

Outcome: Primary outcome was all cause mortality

Results: No significant difference in survival or hazard ratio between NHD and DTX. Significant survival benefit for patients undergoing LTX versus NHD. Significant mortality hazard ratio reduction with LTX (0.51) with no difference in hazard ratio for DTX versus NHD reference.

Conclusion: NHD has comparable mortality to DTX, but is inferior to LTX.

**Features of Nephritic Syndrome****PHAROH**

Proteinuria
Hematuria
Azotemia
RBC casts
Oliguria
Hypertension

- RBC casts and/or dysmorphic RBCs in urine
- oliguria
- HTN (due to salt and water retention)
- puffy eyes
- smoky urine

Etiology

- etiology can be divided into low and normal complement levels (Table 10)
- frequently immune-mediated, with Ig and C3 deposits found in GBM
- outcome dependent on etiology

Table 10. Etiology of Nephritic Syndrome

	Low Complement Level	Normal Complement Level
Primary Causes	Postinfectious GN Membranoproliferative GN	IgA nephropathy Anti-GBM disease
Secondary Causes	SLE Endocarditis Abscess or shunt nephritis Cryoglobulinemia	Polyarteritis nodosa Wegener's granulomatosis Henoch-Schönlein purpura Goodpasture's syndrome

2. NEPHROTIC SYNDROME**Clinical/Lab Features**

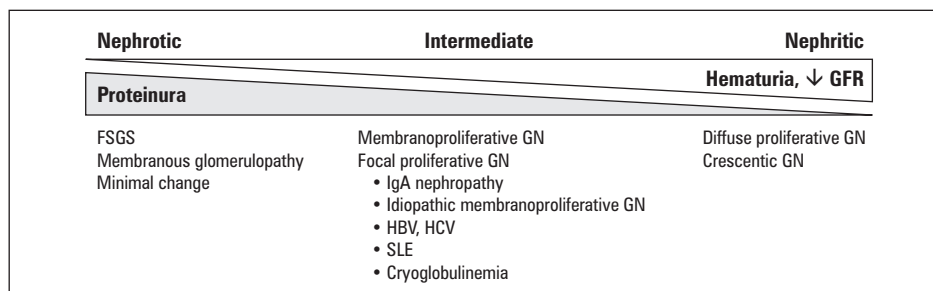
- heavy proteinuria ($>3.5 \text{ g}/1.73\text{m}^2/\text{d}$)
- hypoalbuminemia
- edema
- hyperlipidemia (elevated LDL cholesterol), lipiduria (fatty casts and oval fat bodies on microscopy)
- hypercoagulable state (due to antithrombin III, Protein C and Protein S urinary losses)
- patient may report frothy urine
- glomerular pathology on renal biopsy:
 - minimal change disease (or minimal lesion disease or nil disease) – i.e. glomeruli appear normal on light microscopy
 - membranous glomerulopathy
 - focal segmental glomerulosclerosis (FSGS)
 - membranoproliferative glomerulonephritis
 - nodular glomerulosclerosis
- each can be idiopathic or secondary to a systemic disease or drug (sirolimus can cause proteinuria without obvious glomerular pathology)

Table 11. Nephrotic Syndrome

	Minimal Change	Membranous Glomerulopathy	Focal Segmental Glomerulosclerosis	Membranoproliferative Glomerulonephritis	Nodular Glomerulosclerosis
Secondary Causes	Hodgkin's lymphoma	HBV, SLE, solid tumours (lung, breast, GI)	Reflux nephropathy, HIV, HBV, obesity	HCV, malaria, SLE, leukemia, lymphoma, infected shunt	Diabetes mellitus, amyloidosis
Drug Causes	NSAIDs	Gold, penicillamine	Heroin		
Therapy	Steroids	Reduce BP, ACEI, steroids	Steroids, ACEI/ARB for proteinuria	Aspirin, ACEI, dipyridamole (Persantine®) – controversial	Treat underlying cause

The Nephritic-Nephrotic Spectrum

- glomerular pathology can present with a clinical picture anywhere on a spectrum with pure nephritic and pure nephrotic syndromes at the extremes (see Figure 15)

**Figure 15. The Spectrum of Glomerular Pathology****Presentation of Nephrotic Syndrome**

1. Severe proteinuria ($>3.5 \text{ g}/\text{d}$)
2. Hypoalbuminemia
3. Edema
4. Hyperlipidemia, lipiduria
5. Oval fat bodies (microscopy)
6. Hypercoagulable state (antithrombin III, protein C and protein S lost in urine)

3. RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN)

Clinical/Lab Features

- a subset of nephritic syndrome in which renal failure progresses in weeks to months
- crescent formation usually seen on renal biopsy
- RBC casts and/or dysmorphic RBCs in urine
- classified by immunofluorescence staining (see Table 12)
- treatment: underlying cause for postinfectious; corticosteroids + cyclophosphamide or other cytotoxic agent + plasmapheresis in select cases
- prognosis: 50% recovery with early treatment, depends on underlying cause

Table 12. RPGN Classification

	RPGN Type I: Anti-GBM mediated	RPGN Type II: Immune Complex mediated	RPGN Type III: Non-immune mediated (i.e. pauci-immune)
% of RPGN Cases	15% of cases	24% of cases	60% of cases
Immuno-fluorescence Staining Pattern	Linear pattern due to IgG and C3 deposition along capillary loops	Granular pattern due to subendothelial or subepithelial deposits of IgG and C3	No immune staining
Pathogenesis	Antibodies against type IV collagen in GBM	Most often 2° to systemic disease	Vasculitis of glomerular capillaries
Primary Causes	Idiopathic anti-GBM disease	IgA nephropathy	Idiopathic
Secondary Causes	Goodpasture's disease	Post-infectious GN, SLE, Cryoglobulinemia, Henoch-Schonlein purpura	Wegener's (c-ANCA +ve) Microscopic polyangiitis (p-ANCA +ve) Churg-Strauss (ANCA -ve)

4. ASYMPTOMATIC URINARY ABNORMALITIES

Clinical/Lab Features

- isolated proteinuria (usually <2 g/day) and/or isolated microscopic or macroscopic hematuria
 - isolated proteinuria
 - ♦ can be postural
 - ♦ occasionally can signal beginning of more serious GN (e.g. FSGS, IgA nephropathy, amyloid, diabetic nephropathy)
 - hematuria with or without proteinuria
 - ♦ IgA nephropathy (Berger's disease): most common type of primary glomerular disease worldwide, usually presents after viral URTI
 - ♦ hereditary nephritis (Alport's disease): X-linked nephritis often associated with sensorineural hearing loss; proteinuria <2 g/day
 - ♦ thin basement membrane disease: usually autosomal dominant, without proteinuria; benign
 - ♦ benign recurrent hematuria: hematuria associated with febrile illness, exercise or immunization; a diagnosis of exclusion after other possibilities are ruled out

Investigations for Glomerular Disease

- blood work
 - first presentation: electrolytes, Cr, urea, albumin, fasting lipids
 - determining etiology: CBC, ESR, serum immunoelectrophoresis, C3, C4, ANA, p-ANCA, c-ANCA, cryoglobulins, HBV and HCV serology, ASOT (anti-streptolysin titres), VDRL, HIV
- urinalysis: RBCs, WBCs, casts, protein
- 24-hr urine for protein and CrCl
- radiology
 - CXR (infiltrates, CHF, pleural effusion)
 - renal ultrasound
- renal biopsy (percutaneous or open) if heavy proteinuria or renal insufficiency, and cause not obviously diabetic nephropathy
- urine immunoelectrophoresis
 - for Bence-Jones protein if proteinuria present

Secondary Causes of Glomerular Disease

EULAR Recommendations for the Management of Systemic Lupus Erythematosus (SLE)

Ann Rheum Dis 2008; 67:195-205

Lupus Nephritis Recommendations

Monitoring: Renal biopsy, urine sediment analysis, proteinuria, and kidney function may have independent predictive ability for clinical outcome in therapy of lupus nephritis but need to be interpreted in conjunction. Changes in immunological tests (anti-dsDNA, serum C3) have only limited ability to predict the response to treatment and may be used only as supplemental information.

Treatment: In patients with proliferative lupus nephritis, glucocorticoids in combination with immunosuppressive agents are effective against progression to end-stage renal disease. Long-term efficacy has been demonstrated only for cyclophosphamide-based regimens, which are however associated with considerable adverse effects. In short- and medium-term trials, mycophenolate mofetil has demonstrated at least similar efficacy compared with pulse cyclophosphamide and a more favourable toxicity profile: failure to respond by 6 months should evoke discussions for intensification of therapy. Flares following remission are not uncommon and require diligent follow-up.

End-stage renal disease: Dialysis and transplantation in SLE have rates for long-term patient and graft-survival comparable with those observed in non-diabetic non-SLE patients, with transplantation being the method of choice.

Amyloidosis

- nodular deposits of amyloid in mesangium, usually related to amyloid light chain (AL)
- presents as nephrotic range proteinuria with progressive renal insufficiency
- can be primary or secondary
- secondary causes: multiple myeloma, TB, rheumatoid arthritis, malignancy

Systemic Lupus Erythematosus (Figure 16)

- lupus nephritis can present as any of the glomerular syndromes
- nephrotic syndrome with an active sediment is most common presentation
- glomerulonephritis caused by immune complex deposition in capillary loops and mesangium with resulting renal injury
- serum complement levels are usually low during periods of active renal disease
- children and males with SLE are more likely to develop nephritis

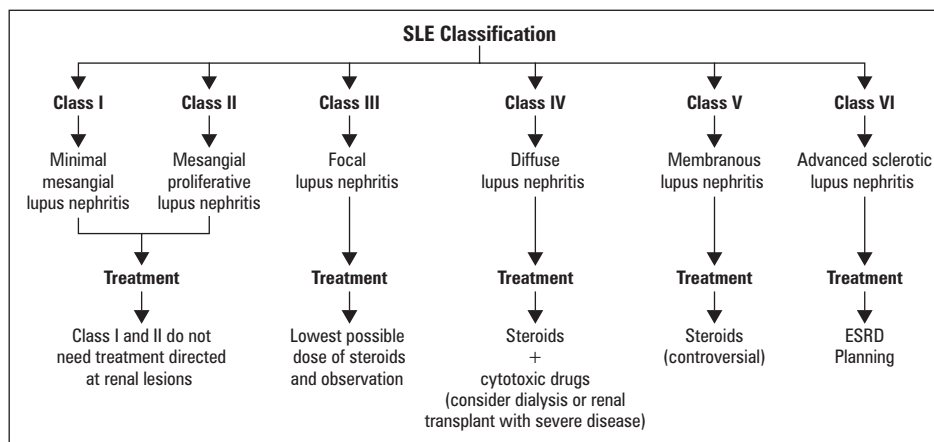


Figure 16. International Society of Nephrology/Renal Pathology Society Classification of Lupus Nephritis 2003

HIV-Associated Renal Disease

1. direct nephrotoxic effect of HIV infection, antiretroviral drugs (e.g. tenofovir, indinavir) and other drugs used to treat HIV-associated infections
2. HIV-associated nephropathy
 - histology: focal and segmental glomerular collapse with mesangial sclerosis, “collapsing FSGS”
 - tubular cystic dilation and tubulo-reticular inclusions
 - clinical features: predominant in black men, heavy proteinuria, progressive renal insufficiency
 - prognosis: kidney failure within one year without treatment
 - therapy: short-term, high dose steroids, ACEI, HAART

Henoch-Schönlein Purpura (HSP)

- seen more commonly in children
- purpura on buttocks and legs, abdominal pain, arthralgia and fever
- glomeruli show varying degrees of mesangial hypercellularity
- IgA and C3 staining of mesangium
- usually benign, self-limiting course; 10% progress to CRF

Goodpasture's Disease

- antibodies against type IV collagen present in lungs and GBM
- more common in 3rd and 6th decades of life, men slightly more affected than females
- present with RPGN type I and hemoptysis/dyspnea
- pulmonary hemorrhage more common in smokers and males
- treat with plasma exchange, cyclophosphamide, prednisone

Wegener's Granulomatosis

- 80% of patients have renal involvement
- focal segmental necrotizing RPGN with no immune staining
- majority of patients with renal disease are c-ANCA positive
- may be indolent or fulminant in progression
- vasculitis and granulomas rarely seen on renal biopsy
- treating with cyclophosphamide, prednisone or sulfa may prevent recurrence

Cryoglobulinemia

- cryoglobulins: monoclonal IgM and polyclonal IgG
- presents as purpura, fever, Raynaud's phenomenon and arthralgias
- at least 50% of patients have hepatitis C
- renal disease seen in 40% of patients (isolated proteinuria/hematuria progressing to nephritic syndrome)
- most patients have decreased serum complement (C4 initially)
- treat hepatitis C, plasmapheresis
- overall prognosis: 75% renal recovery

Infections and Glomerular Disease

Shunt Nephritis

- immune-complex mediated nephritis associated with chronically infected ventriculoatrial shunts inserted for treatment of hydrocephalus
- presents as acute nephritic syndrome with decreased serum complement
- nephrotic range proteinuria in 25% of patients

Infective Endocarditis

- manifests as mild form of acute nephritic syndrome with decreased serum complement
- *S. aureus* is most common infecting agent
- treatment with appropriate antibiotics usually resolves GN

Hepatitis B

- membranous GN, polyarteritis nodosa, membranoproliferative GN

Hepatitis C

- membranoproliferative GN, cryoglobulinemia

Syphilis

- membranous GN

Malaria

- variable glomerular involvement

Tubulointerstitial Disease

Tubulointerstitial Nephritis (TIN)

**Definition**

- cellular infiltrates affecting primarily the renal interstitium and tubular cells
- functional tubule defects are disproportionately greater than the decrease in GFR
- classified as acute or chronic

Signs and Symptoms

- manifestation of disease depends on site of tubule affected
 1. proximal tubule (e.g. multiple myeloma, heavy metals)
 - ♦ Fanconi syndrome: decreased reabsorption in proximal tubule causing glycosuria, aminoaciduria, phosphaturia, hypouricemia
 - ♦ proximal RTA (decreased bicarbonate absorption): Type II RTA
 2. distal tubule (e.g. amyloidosis, obstruction)
 - ♦ distal RTA (Type I RTA)
 - ♦ Na-wasting nephropathy
 - ♦ \pm hyperkalemia, type IV RTA
 3. collecting duct (e.g. sickle cell anemia, analgesics, PCKD)
 - ♦ urine concentrating defect
 - ♦ polyuria (nephrogenic DI)

1. ACUTE TUBULOINTERSTITIAL NEPHRITIS

Definition

- rapid (days to weeks) decline in renal function
- 10-20% of all acute kidney injury

Etiology

- hypersensitivity
 1. antibiotics: beta-lactams, sulfonamides, rifampin, quinolones, cephalosporins
 2. other: NSAIDs, allopurinol, furosemide
- infections
 - bacterial pyelonephritis, *Streptococcus*, brucellosis, *Legionella*, CMV, EBV, toxoplasmosis, leptospirosis
- immune
 - SLE, acute allograft rejection, Sjögren's syndrome, sarcoidosis, mixed essential cryoglobulinemia
- idiopathic

Pathophysiology

- acute inflammatory cell infiltrates into renal interstitium

Signs and Symptoms

- acute renal failure
- if hypersensitivity reaction: may see fever, skin rash, arthralgia, serum sickness-like syndrome
- if pyelonephritis: flank pain and costo-vertebral angle (CVA) tenderness
- other signs and symptoms based on underlying etiology
- hypertension and edema are uncommon

Investigations

- urine
 - sterile pyuria, WBC casts, mild proteinuria, hematuria
 - eosinophils if allergic interstitial nephritis
- blood
 - increased Cr and urea
 - eosinophilia if drug reaction
 - normal PAG metabolic acidosis (renal tubular acidosis)
 - hypophosphatemia, hyperkalemia, hyponatremia
- gallium scan shows intense signal due to inflammatory infiltrate
- renal biopsy definitive

Treatment

- treat underlying cause (e.g. stop offending medications, antibiotics if pyelonephritis)
- corticosteroids (may be indicated in allergic or immune disease)

Prognosis

- recovery within 2 weeks if underlying insult can be eliminated

2. CHRONIC TUBULOINTERSTITIAL NEPHRITIS**Definition**

- characterized by slowly progressive renal failure, moderate proteinuria and signs of abnormal tubule function

Etiology

- persistence or progression of acute TIN
- urinary tract obstruction: most important cause of chronic TIN
- chronic pyelonephritis: due to vesicoureteral reflux or UTI with obstruction
- nephrotoxins
 - exogenous
 - ♦ analgesics: NSAIDs (common), acetaminophen
 - ♦ cisplatin, lithium, cyclosporine, tacrolimus
 - ♦ heavy metals (lead, cadmium, copper), lithium, mercury, arsenic
 - ♦ radiation
 - ♦ chinese herbs
 - endogenous
 - ♦ hypercalcemia, hypokalemia, oxalate, uric acid nephropathy
- vascular disease: ischemic nephrosclerosis, atheroembolic disease
- malignancies: multiple myeloma
- granulomatous: TB, sarcoidosis, Wegener's granulomatosis
- immune: SLE, Sjögren's, cryoglobulinemia, Goodpasture's, amyloidosis, renal graft rejection
- hereditary: cystic diseases of the kidney, sickle cell disease
- others: radiation, Balkan (endemic) nephropathy

Pathophysiology

- fibrosis of interstitium with atrophy of tubules, mononuclear cell inflammation

Signs and Symptoms

- tubular dysfunction (e.g. acidosis, electrolyte disturbances)
- progressive renal failure with azotemia and uremia
- dependent on underlying etiology

Treatment

- stop offending agent or treat underlying disease
- supportive measures: correct metabolic disorders (Ca, PO₄) and anemia

Findings which Suggest Chronic Tubulointerstitial Nephritis

- normal PAG metabolic acidosis
- hyperkalemia (out of proportion to degree of renal insufficiency)
- polyuria, nocturia
- partial or complete Fanconi's syndrome
- urine: mild proteinuria, few RBCs and WBCs, no RBC casts
- ultrasound: shrunken kidneys with irregular contours

Acute Tubular Necrosis (ATN)

Definition

- abrupt and sustained decline in GFR within minutes to days after ischemic/nephrotoxic insult
- GFR shuts down to avoid life-threatening loss of electrolytes from non-functioning tubules

Etiology

- see Figure 17

Clinical Presentation

- typically presents as an abrupt rise in urea and Cr after a hypotensive episode, sepsis, rhabdomyolysis, or administration of nephrotoxic drug
- urine: high FE_{Na}, pigmented-granular casts

Complications

- hyperkalemia: can occur rapidly and cause serious arrhythmia
- metabolic acidosis, decreased Ca, increased PO₄, hypoalbuminemia

Investigations

- blood: CBC, electrolytes, Cr, urea, Ca, PO₄, blood gases
- urine: R&M, electrolytes, osmolality
- ECG
- abdominal ultrasound

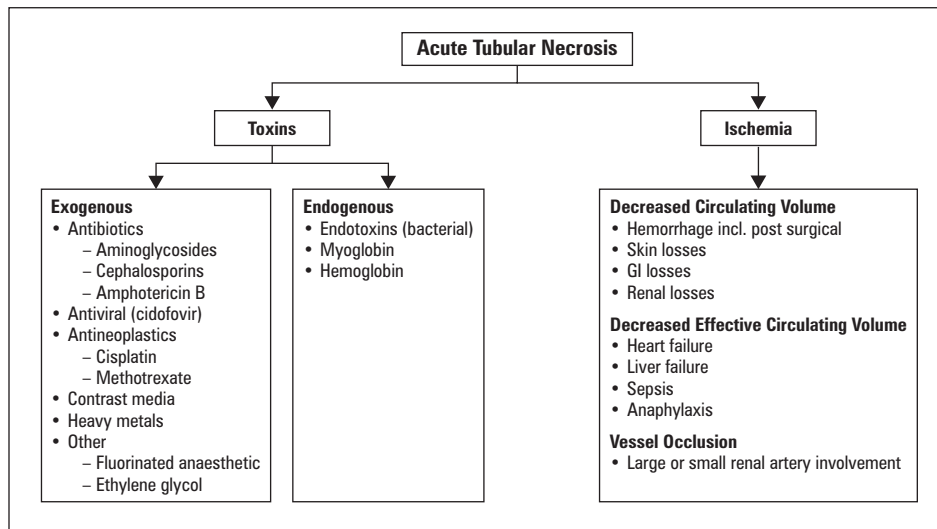


Figure 17. Etiology of ATN

Meta-analysis: Effectiveness of Drugs for Preventing Contrast-induced Nephropathy*Ann Intern Med* 2008; 19;148:284-94

Purpose: To determine the effectiveness of N-acetylcysteine, theophylline, fenoldopam, dopamine, iloprost, statin, furosemide, or mannitol on preventing nephropathy.

Study Selection: Only randomized, controlled trials that used these agents in patients receiving iodinated contrast.

Results: In the 41 RCTs included N-acetylcysteine (RR = 0.62 [0.44-0.88]) and Theophylline (RR = 0.49 [0.23-1.06]) reduced the risk of nephropathy more than saline alone. Furosemide increased the risk (RR = 3.27 [1.48-7.26]). Other agents did not affect risk of nephropathy.

Conclusion: N-acetylcysteine is more renoprotective than hydration alone.

Therapy

- largely supportive once underlying problem is corrected
- loop diuretics may help manage volume overload and reduce tubular metabolic requirements to allow for recovery (controversial)
- consider early dialysis in severe/rapidly progressing cases to prevent uremic syndrome

Prevention

- correct fluid balance before surgical procedures
- for patients with chronic renal disease requiring radiographic contrast: give N-acetylcysteine 600-1200 mg PO bid day before and day of procedure
- use renal-adjusted doses of nephrotoxic drugs in patients with renal insufficiency
- isotonic NaHCO_3 at 3 ml/kg over 1h before procedure and 1 ml/kg/h for 6h post-procedure if not contraindicated
- avoid giving diuretics, ACE inhibitors, cyclosporine on morning of procedure if possible

Analgesic Nephropathies

1. Vasomotor Acute Kidney Injury (AKI)

- normally prostaglandins vasodilate renal arterioles to maintain blood flow
- NSAIDs act by blocking cyclooxygenase enzyme, thereby preventing prostaglandin synthesis and causing renal ischemia
- more common in elderly, underlying renal disease, hypovolemia (diuretics, CHF, cirrhosis, nephrotic syndrome)
- clinically: develop prerenal azotemia within a few days of starting NSAID
- treatment: discontinue NSAID, dialysis rarely needed

2. Acute Interstitial Nephritis (AIN)

- majority due to fenoprofen (60%), ibuprofen, naproxen
- may be associated with minimal change glomerulopathy and nephrotic range proteinuria
- resolves eventually with discontinuation of NSAID, may require interval dialysis
- short term high dose steroids (1 mg/kg/day of prednisone) may hasten recovery

3. Chronic Interstitial Nephritis

- due to excessive consumption of antipyretics (phenacetin or acetaminophen) in combination with NSAIDs
- associated with emotional stress, psychiatric symptoms and GI disturbance
- papillary necrosis
 - gross hematuria, flank pain, declining renal function
 - calyceal filling defect seen with IVP – “ring sign”
- increased risk of transitional cell carcinoma of renal pelvis
- good prognosis if discontinue analgesics

4. Acute Tubular Necrosis (ATN)

- incidence of renal dysfunction is related to the severity of acetaminophen ingestion
- vascular endothelial damage can also occur
- both direct toxicity and ischemia contribute to the tubular damage
- renal function spontaneously returns to baseline within 1-4 weeks
- dialysis may be required during the acute episode of ingestion

5. Other Effects of NSAIDs

- sodium retention (2° to reduced GFR)
- hyperkalemia, HTN (2° to hyporeninemic hypoaldosteronism)
- excess water retention (due to elimination of ADH – antagonistic effect of prostaglandins)

Vascular Diseases of the Kidney

Large Vessel Disease

1. RENAL ARTERY OCCLUSION

- important, potentially reversible cause of renal failure

Etiology

- abdominal trauma, surgery, embolism, vasculitis, extrarenal compression, hypercoagulable state, aortic dissection
- kidney transplant more vulnerable

Signs and Symptoms (depend on presence of collateral circulation)

- fever, nausea, vomiting, flank pain
- leukocytosis, elevated AST, LDH, ALP
- acute onset hypertension (activation of RAAS) or sudden worsening of long-standing hypertension
- renal dysfunction (if bilateral, or solitary functioning kidney)

Investigations

- renal arteriography (more reliable but risk of contrast-mediated ATN, atheroembolic renal disease)
- contrast-enhanced CT or magnetic resonance angiography, duplex Doppler studies (operator dependent)

Treatment

- prompt localization of occlusion and restoration of blood flow
- anticoagulation, thrombolysis, percutaneous angioplasty or clot extraction, surgical thrombectomy

2. ISCHEMIC RENAL DISEASE (RENAL ARTERY STENOSIS)

- chronic renal impairment secondary to hemodynamically significant renal artery stenosis or microvascular disease
- significant cause of ESRD: 15% in patients over 50 years old (higher prevalence if significant vascular disease)
- usually associated with large vessel disease elsewhere
- causes
 1. atherosclerosis – more common in elderly
 2. fibromuscular dysplasia – more common in females, age 30-50

Risk Factors

- >50 years old
- smoking
- other atherosclerotic disease
- severe/refractory HTN and/or hypertensive crises
- asymmetrical renal size
- increasing Cr with ACEI/ARB
- flash pulmonary edema with normal LV function

Investigations

- must establish presence of renal vessel stenosis and prove it is responsible for renal dysfunction
- duplex Doppler U/S (kidney size, blood flow): good screening test (operator dependent)
- CT or MR angiography (effective noninvasive tests to establish presence of stenosis)
- ACE inhibitor renography (i.e. captopril renal scan)
- renal arteriography (gold standard)

Treatment

- medical therapy, percutaneous angioplasty + stent, surgical revascularization
- little or no benefit if therapy is late i.e. kidney is already shrunken. However, therapy can be considered to save the opposite kidney if normal

3. RENAL VEIN THROMBOSIS**Etiology**

- hypercoagulable states (e.g. nephrotic syndrome, especially membranous), ECF volume depletion, extrinsic compression of renal vein, significant trauma, malignancy (e.g. RCC), sickle cell
- clinical presentation determined by rapidity of occlusion and formation of collateral circulation
- acute: nausea/vomiting, flank pain, hematuria, elevated plasma LDH, \pm rise in Cr, sudden rise in proteinuria
- chronic: increasing proteinuria and/or tubule dysfunction

Investigations

- renal venography (gold standard), CT or MR angiography, duplex Doppler U/S

Treatment

- anticoagulation with heparin then warfarin (1 yr or indefinitely, depending on risk factors)

Revascularization versus Medical Therapy for Renal-Artery Stenosis

NEJM 2009; 361:1953-62

Study: Multi-center, un-blinded RCT, median follow-up of 34 months

Patients: 806 patients (mean age 70) with atherosclerotic stenosis in at least one renal artery and uncertain clinical benefit of revascularization. Intervention: Percutaneous revascularization (angioplasty and/or stenting) with medical therapy (i.e. statins, antiplatelet, BP control) versus medical therapy alone

Outcomes: Primary outcome was change in renal function (slope of creatinine concentration over time). Secondary outcomes include BP, time to first renal event, time to first CV event, and mortality.

Results: No significant difference in change of renal function between intervention and medical therapy control. No significant differences in any secondary outcomes were found between revascularization and medical therapy control. 31 patients (9%) experienced a periprocedural complication, and 55 patients (20%) experienced a post-procedural complication.

Conclusion: Renal artery revascularization carries significant risks without any benefit to renal function or secondary outcomes compared to medical therapy

Small Vessel Disease

1. HYPERTENSIVE NEPHROSCLEROSIS

- see *Hypertension*, NP32

2. ATHEROEMBOLIC RENAL DISEASE

- progressive renal insufficiency due to embolic obstruction of small and medium-sized renal vessels by atheromatous emboli
- spontaneous or after renal artery manipulation (surgery, angiography, percutaneous angioplasty)
- anticoagulants and thrombolytics interfere with ulcerated plaque healing and can worsen disease
- presentation: acute or chronic, progressive renal dysfunction, labile hypertension, extrarenal atheroembolic disease support diagnosis (livedo reticularis is a classic sign)
- pathology: needle-shaped cholesterol clefts (due to tissue-processing artifacts) with surrounding tissue reaction in small/medium-sized vessels
- no effective treatment; avoid angiographic and surgical procedures in patients with diffuse atherosclerosis

3. THROMBOTIC MICROANGIOPATHY

- a spectrum which includes HUS, TTP, DIC, post-partum renal failure
- renal involvement more common in HUS than TTP
- renal involvement characterized by fibrin thrombi in glomerular capillary loops \pm arterioles
- treatment:
 - depends on cause
 - supportive therapy
 - TTP: plasma exchange, corticosteroids (splenectomy and rituximab if refractory)
- avoid platelet transfusions and ASA

4. SCLERODERMA

- 50% scleroderma patients have renal involvement (mild proteinuria, high Cr, HTN)
- histology: media thickened, "onion skin" hypertrophy of small renal arteries, fibrinoid necrosis of afferent arterioles and glomeruli
- 10-15% scleroderma patients have a "scleroderma renal crisis": malignant HTN (usually within the first few years), ARF, microangiopathy, volume overload, visual changes, HTN encephalopathy
- renal involvement usually occurs early in the course of illness
- treatment: BP control with ACEI slows progression of renal disease

5. CALCINEURIN INHIBITOR NEPHROPATHY

- cyclosporine and tacrolimus
- causes both acute reversible and chronic, largely irreversible nephrotoxicity
- major cause of kidney failure in other solid organ transplant (e.g. heart)
- acute: due to afferent and efferent glomerular capillary constriction leading to decreased GFR (tubular vacuolization)
 - pre-renal azotemia
 - treatment: calcium channel blockers or prostaglandin analogs, reduce dose of cyclosporine or switch to another immunosuppressive drug
- chronic: result of obliterative arteriolopathy causing interstitial nephritis and CRF (striped fibrosis), less frequent now due to lower doses of calcineurin inhibitors

Long-term Outcomes of Scleroderma Renal Crisis

Ann Intern Med 2000; 17;133:600-3

Study: Prospective observational cohort study with follow up of 5-10 years.

Patients: 145 patients with scleroderma renal crisis who received ACE inhibitors and 662 patients with scleroderma who did not have renal crisis.

Primary Outcome: The need for dialysis and early death among patients with renal crisis

Results: Sixty-one percent of patients with renal crisis had good outcomes (55 had no dialysis and 34 received temporary dialysis); only 4 of these patients progressed to chronic renal failure and permanent dialysis. Greater than 50% of the patients who initially required dialysis discontinued it 3 to 18 months later. Permanent dialysis or early death occurred in 39% of the patients.

Conclusion: Renal crisis can be managed when hypertension is aggressively controlled with ACE inhibitors.

Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation (ELITE-Symphony Trial)

NEJM 2007; 257:2562-75

Study: Multicentre, randomized controlled trial with 12 month follow-up.

Patients: 1645 patients scheduled to receive a single organ kidney transplant.

Intervention: Mycophenolate mofetil, corticosteroids and either: 1) standard dose cyclosporine; 2) low dose cyclosporine with daclizumab induction; 3) low dose tacrolimus with daclizumab induction; 4) low dose sirolimus with daclizumab induction.

Primary Outcome: Estimated Cockcroft-Gault GFR 12 months after transplantation.

Results: the Tacrolimus arm showed significantly higher eGFR at 12 months compared to all other arms (65.4 ml/min vs. 57.1, 59.4, 56.7 for arms 1, 2, 4 respectively, $p < 0.001$). The Tacrolimus arm also showed decreased rates of acute rejection at 6 months and 12 months vs. all arms ($p < 0.001$); improved allograft survival against standard dose cyclosporine and sirolimus; and decreased treatment failure against all other arms. There was no difference in overall patient survival between groups. Sirolimus has the highest incidence of lymphoceles, delayed wound healing, and serious adverse events; tacrolimus has significantly higher rates of new-onset diabetes; and cyclosporine regimens had the lowest incidence of diarrhea but highest opportunistic infection rates.

Conclusion: Immunosuppression regimens using low dose tacrolimus and daclizumab induction decrease nephrotoxicity while maintaining therapeutic immunosuppression in renal transplant patients.

Systemic Diseases and the Kidney

Hypertension (HTN)

- HTN occurs in about 20% of population
- etiology classified as primary ("essential"; makes up 90% of cases) or secondary
- diseases of renal parenchyma or renal vasculature can cause secondary hypertension
- conversely, hypertension due to other factors can cause renal disease (hypertensive nephrosclerosis) or worsen pre-existing renal disease

Hypertensive Nephrosclerosis

Table 13. Chronic vs. Malignant Nephrosclerosis

	Chronic Nephrosclerosis	Malignant Nephrosclerosis
Histology	Slow vascular sclerosis with ischemic changes affecting intralobular and afferent arterioles	Fibrinoid necrosis of arterioles, disruption of vascular endothelium
Clinical Picture	African American, underlying chronic kidney disease, chronic hypertensive disease	Acute elevation in BP (dBP > 120 mmHg) HTN encephalopathy
Urinalysis	Mild proteinuria, normal urine sediment	Proteinuria and hematuria (RBC casts)
Therapy	Blood pressure control, frequent follow-up	Lower dBP to 100-110 mmHg within 6-24 hours More aggressive treatment can cause ischemic event Identify and treat underlying cause of HTN
Prognosis	Can progress to renal failure despite patient adherence	Lower survival if renal insufficiency develops

Renovascular Hypertension

- HTN caused by renovascular disease
- 1-2% of all hypertensive patients, most common cause of secondary hypertension
- suspect if
 - negative family history of HTN
 - sudden onset or exacerbation of HTN
 - difficult to control with antihypertensive therapy
 - epigastric or flank bruit
 - spontaneous hypokalemia (renin activation from underperfused kidney)
 - history of diffuse atherosclerosis

Etiology and Classification

- decreased renal perfusion of one or both kidneys leads to increased renin release and subsequent angiotensin production
- increased angiotensin raises blood pressure in 2 ways
 1. causes generalized arteriolar constriction
 2. release of aldosterone increases Na and water retention
- elevated blood pressure can in turn lead to further damage of kidneys and worsening HTN
- 2 types of renovascular HTN (RAS)
 - atherosclerotic plaques: proximal 1/3 renal artery, usually males >55 years, smokers
 - fibromuscular hyperplasia: distal 2/3 renal artery or segmental branches, usually young females
- patients with bilateral renal artery stenosis are at risk of ARF with ACEI or NSAIDs
 - when there is decreased renal blood flow (RBF), GFR is dependent on A_{II}-induced efferent arteriolar constriction which raises filtration fraction (GFR/RBF)

Investigations

- renal U/S and Dopplers
- digital subtraction angiography (risk of contrast nephropathy)
- renal scan before and after ACEI (accentuates difference in GFR)
- MR angiography (avoid gadolinium contrast if eGFR <30 ml/min because of risk of systemic dermal fibrosis)
- gold standard is arterial angiography

Treatment

- BP lowering medications (ACEI is drug of choice if unilateral renal artery disease but contraindicated if bilateral renal artery disease)
- angioplasty ± stent
- angioplasty for simple fibromuscular dysplasia lesion in young patients
- occasionally surgical bypass

Renal Parenchymal Hypertension

- HTN caused secondary to GN, AIN, diabetic nephropathy, or any other chronic renal disease
- mechanism of HTN not fully understood but may include
 - excess renin-angiotensin-aldosterone system activation due to inflammation and fibrosis in multiple small intra-renal vessels
 - production of unknown vasopressors, lack of production of unknown vasodilators, or lack of clearance of endogenous vasopressor
 - ineffective sodium excretion with fluid overload

Investigations

- as well as investigations for renovascular HTN, additional tests may include
 - 24-hour urinary estimations of Cr clearance and protein excretion
 - imaging (U/S, CT, radionuclide scan)
 - serology for collagen-vascular disease
 - renal biopsy

Treatment

- most chronic renal disease is irreversible, but treatment of HTN can slow the progression of renal insufficiency
- control ECF volume: Na restriction (88 mmol/day intake), diuretic, dialysis with end-stage disease
- ACE inhibitor and/or ARB may provide added benefit (monitor K and Cr)

Multiple Myeloma



Features of Multiple Myeloma

CARLI

Calcium (elevated)
Anemia
Renal Failure
Lytic Bone Lesions
Infections

- malignant proliferation of plasma cells in the bone marrow with the production of immunoglobulins
- patients may present with severe bone disease and renal failure
- light chains are filtered at the glomerulus and appear as Bence-Jones proteins in the urine (monoclonal light chains)
- kidney damage can occur by several mechanisms:
 - hypercalcemia
 - light chain cast nephropathy (LCCN) or “myeloma kidney”
 - hyperuricemia
 - infection
 - secondary amyloidosis
 - monoclonal Ig deposition disease (MIDD)
 - diffuse tubular obstruction
- LCCN
 - large tubular casts in urine sediment (light chains + Tamm-Horsfall protein)
 - proteinuria and renal insufficiency, can progress rapidly to kidney failure
- MIDD
 - deposits of monoclonal Ig in kidney, liver, heart and other organs
 - mostly light chains (85-90%)
 - causes nodular glomerulosclerosis (similar to diabetic nephropathy)
- lab features: increased BUN, increased Cr, urine protein immunoelectrophoresis positive for Bence-Jones protein (not detected on urine dipstick)
- poor candidates for kidney transplantation

Malignancy

- cancer can have many different nephrological manifestations
- kidney transplantation cannot be performed unless malignancy is cured
 - solid tumours: mild proteinuria or membranous GN
 - lymphoma: minimal change GN (Hodgkin's) or membranous GN (non-Hodgkin's)
 - renal cell carcinoma
 - tumour lysis syndrome: hyperuricemia, diffuse tubular obstruction
 - chemotherapy (especially cisplatin): ATN or chronic TIN
 - pelvic tumours/mets: post-renal failure secondary to obstruction
 - 2° amyloidosis
 - radiotherapy (radiation nephritis)

Diabetes and the Kidney

- diabetic nephropathy: presence of microalbuminuria or overt nephropathy in patients with DM who lack indicators of other renal diseases
- most common cause of end-stage renal failure in North America
- 35-50% of Type 1 will develop nephropathy, unknown percentage of Type 2
- at diagnosis up to 30% of Type 2 have albuminuria (75% microalbuminuria, 25% overt nephropathy)
- microalbuminuria is a risk factor for progression to overt nephropathy and cardiovascular disease
- once proteinuria is established, renal function declines, 50% patients reach ESRD within 7-10 years



DM is one of the causes of ESRD that does not result in small kidneys at presentation of ESRD. The others are amyloidosis, HIV nephropathy, PCKD and multiple myeloma.



Abnormal Urine ACR Values from 2008 Canadian Diabetes Association CPG
>2.0 mg/mmol in males
>2.8 mg/mmol in females

- associated with HTN and diabetic retinopathy (especially Type 1 diabetes) and/or neuropathy (especially Type 2 diabetes)
- indication of possible nondiabetic renal disease in diabetic patients
 - rising Cr with little/no proteinuria
 - lack of retinopathy or neuropathy (microvascular complications)
 - persistent hematuria (microscopic or macroscopic)
 - signs or symptoms of systemic disease
 - inappropriate time course; rapidly rising Cr, short duration of DM
 - family history of nondiabetic renal disease (e.g. PCKD, Alport's)

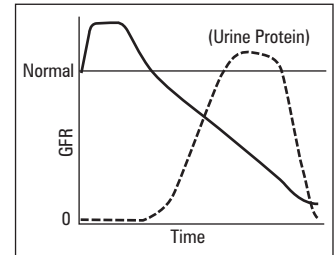


Figure 18. GFR and Urine Protein over Time in Diabetes



ACEI can cause hyperkalemia. Therefore, be sure to watch serum K, especially if patient has DM and renal insufficiency.

DIABETIC RENAL COMPLICATIONS

1. Progressive Glomerulosclerosis

- classic diabetic glomerular lesion: Kimmelstiel-Wilson nodular glomerulosclerosis (15-20%)
- more common lesion is diffuse glomerulosclerosis with a uniform increase in mesangial matrix
- stage 1
 - **increased GFR** (120-150%) – compensatory hyperfiltration of remaining nephrons
 - \pm slightly increased mesangial matrix
- stage 2
 - **detectable microalbuminuria** (between 0-300 mg/24 hours)
 - **Albumin-Creatinine ratio (ACR)** 2.0–20 mg/mmol in men (18-180 mg/d), 2.8-28 mg/mmol in women (25-250 mg/d)
 - increased mesangial matrix
- stage 3
 - **macroalbuminuria** (>300 mg/24h); **ACR** in men >20 mg/mmol, (>180 mg/d); in women, **ACR** is >28 mg/mmol (>250 mg/d)
 - **clinically detectable proteinuria**, +ve urine dipstick
 - normal GFR
 - very expanded mesangial matrix
- stage 4
 - **increased proteinuria** (>500 mg/24hr)
 - decreased GFR
 - <20% glomerular filtration surface area present
 - sclerosed glomeruli

2. Accelerated Atherosclerosis

- common finding
- decreased GFR
- may increase Angiotensin II production resulting in increased BP
- increased risk of ATN secondary to contrast media

3. Autonomic Neuropathy

- affects bladder leading to functional obstruction and urinary retention
- residual urine promotes infection
- obstructive nephropathy

4. Papillary Necrosis

- Type 1 DM susceptible to ischemic necrosis of medullary papillae
- sloughed papillae may obstruct ureter
- can present as renal colic or with obstructive features \pm hydronephrosis

2008 Canadian Diabetics Association Clinical Practice Guidelines on Chronic Kidney Disease in Diabetes

- screen for microalbuminuria with a random urine test for albumin to Cr ratio (ACR) and eGFR with a serum creatinine (e.g. using MDRD equation)
 - Type 1 DM: annually in adults after 5 years with diagnosis
 - Type 2 DM: at diagnosis then annually
 - must have at least 2/3 abnormal ACRs to diagnose nephropathy
 - with DM and CKD: urine ACR and serum Cr (for eGFR) every 6 months
 - delay screening if transient cause of albuminuria or low eGFR
- evaluate for other causes of proteinuria, rule out nondiabetic renal disease
- avoid unnecessary potential nephrotoxins (NSAIDs, aminoglycosides, dye studies)

Renoprotective Effect of Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes.

NEJM 2001; 345:851-860

Study: Multi-center, RCT, mean follow-up of 2.6 years.

Patients: 806 patients (mean age 70) with T2DM, HTN, and nephropathy (24hr proteinuria >900 mg, serum Creatinine (Cr) 88(Male)/106(Female)-265 μ mol/L)

Intervention: BP control with Irbesartan vs. Amlodipine vs. Placebo, with use of adjuncts (not including ACEs, ARBs, or CCI) as needed.

Outcomes: Primary composite endpoint included doubling of serum Cr, ESRD, or death. Secondary composite endpoint included morbidity and mortality from CVD causes.

Results: BP control was similar in all three arms. Irbesartan had a relative risk reduction of 20% vs. placebo and 23% vs. amlodipine for the primary end point. The Irbesartan group had a 33% risk reduction vs. placebo and 37% reduction vs. amlodipine for risk of doubling serum Cr. Serum Cr increased more slowly in the Irbesartan group versus placebo or amlodipine. No difference in absolute mortality or secondary end point.

Conclusion: Irbesartan conferred significant renoprotective benefits in patients with type 2 diabetes and nephropathy, independent of blood pressure lowering effects.

Renal Outcomes with Telmisartan, Ramipril, or Both in People at High Vascular Risk (ONTARGET Study)

Lancet 2008; 372:547-553

Study: Prospective, multicentre, double-blind, randomized controlled trial.

Participants: 25,620 patients with median follow-up of 56 months.

Intervention: Patients received either ramipril (10 mg/d; N=8576), telmisartan (80 mg/d; N=8542) or a combination of both drugs (N=8502).

Primary Outcome: Composite of dialysis, doubling of creatinine level, and death.

Results: The number of outcome events was similar for telmisartan (n=1147) and ramipril (1150; HR 1.00, CI 0.92-1.09), but was increased with combination therapy (1233; HR 1.09, 1.01-1.18, p=0.037). The need for dialysis or doubling of serum creatinine, was similar with telmisartan (189) and ramipril (174; HR 1.09, 0.89-1.34) and more frequent with combination therapy (212; HR 1.24, 1.01-1.51, p=0.038). Estimated GFR declined least with ramipril compared with telmisartan or combination therapy (p<0.001). The increase in urinary albumin excretion was less with telmisartan (p=0.004) and combination therapy (p=0.001) than with ramipril.

Conclusion: Renal outcomes were similar in both telmisartan and ramipril monotherapy. Combination therapy reduced proteinuria to a greater extent than monotherapy, but was associated with poorer renal outcomes.

Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 DM and Nephropathy

NEJM 2001; 345:861-869

Study: Randomized, double-blind, placebo-controlled trial with mean follow-up of 3.4 years.

Patients: 1513 patients (mean age 60, 63% male, multi-ethnicity) with NIDDM and nephropathy (urinary albumin:Cr ≥ 300 and serum Cr 115-265 $\mu\text{mol/L}$) on conventional antihypertensives (CCB, diuretics, β -blockers, centrally acting agents).

Intervention: Losartan 50 mg PO OD (could be doubled after 4 weeks) vs. placebo.

Outcomes: Primary endpoints included doubling of serum Cr, ESRD, or death. Secondary endpoints included morbidity and mortality from CVD causes.

Results: Losartan reduced incidence of doubling of serum Cr (RR 25%) and ESRD (RR 28%), but had no effect on risk of death. Benefit exceeded that attributable to BP changes alone. Secondary endpoints were similar, although rate of hospitalization for heart failure was significantly lower with losartan (RR 32%).

Conclusion: Losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy, and was generally well tolerated.

Priorities in the Management of Patients with DM

- vascular protection for all patients with diabetes
 - ACEI, antiplatelet therapy (as indicated)
 - BP control, glycemic control, lifestyle modification, lipid control
 - optimization of BP in patients who are hypertensive
 - treat according to hypertension guidelines
 - renal protection for DM patients with nephropathy (even in absence of HTN)
 - Type 1 DM: ACEI
 - Type 2 DM: CrCl >60 mL/min: ACEI or ARB – CrCl <60 mL/min: ARB
 - 2nd line agents: nondihydropyridine calcium channel blockers (diltiazem, verapamil)
 - ACEI and ARB can be safely used together if needed for control of significant proteinuria (monitor for hyperkalemia and acute rise in creatinine)
- check serum Cr and K levels within 1 week of initiating ACEI or ARB and at time of acute illness
 - serum Cr can safely be allowed to rise up to 30% with initiation of ACEI or ARB, usually stabilizes after 2-4 weeks, monitor for significant worsening of renal function or hyperkalemia
 - if $>30\%$ rise in serum Cr or hyperkalemia, discontinue medication and consider 2nd line agent
 - consider holding ACEI, ARB and/or diuretic with acute illness and in women before becoming pregnant
 - consider referral to nephrologist if ACR >60 mg/mmol, eGFR <30 mL/min, progressive kidney function loss, unable to achieve BP targets or unable to stay on ACEI or ARB

Protein Restriction for Diabetic Renal Disease

Cochrane Database Syst Rev 2007; (4):CD002181

Purpose: To review the effects of dietary protein restriction on the progression of diabetic nephropathy.

Study Selection: Randomised controlled trials (RCTs) and before and after studies of the effects of restricted protein diet on renal function in subjects with diabetes. 12 studies were reviewed.

Results: The risk of end-stage renal disease or death was lower in patients on low-protein diet. In patients with Type 1 diabetes no effect on GFR was noted in the low-protein diet group.

Cystic Diseases of the Kidney

- characterized by epithelium-lined cavities filled with fluid or semisolid debris within the kidneys
- includes: simple cysts (present in 50% of population over 50), medullary cystic kidney, medullary sponge kidney, polycystic kidney disease (autosomal dominant and recessive) and acquired cystic kidney disease (in chronic hemodialysis patients)

Adult Polycystic Kidney Disease

- PKD1 (1:400), PKD2 (1:1,000), accounts for about 10% of cases of renal failure
- autosomal dominant; at least 3 genes: PKD1 (chr 16p), PKD2 (chr 4q), PKD3 (location not yet determined)
- polycystin protein from PKD1 responsible for cell-cell and cell-matrix interaction
- defect can lead to abnormal cell growth and cyst formation
- extrarenal manifestations: most common; multiple asymptomatic hepatic cysts (33%), cerebral aneurysm (10%), diverticulosis and mitral valve prolapse (25%)
- polycystic liver disease rarely causes liver failure
- less common: cysts in pancreas, spleen, thyroid, ovary, seminal vesicles, and aorta

Signs and Symptoms

- often asymptomatic; discovered incidentally on imaging or by screening those with FHx
- acute abdominal flank pain/dull lumbar back pain
- hematuria (microscopic frequently initial sign, gross)
- nocturia (urinary concentrating defect)
- rarely extra-renal presentation (e.g. ruptured berry aneurysm, diverticulitis)
- HTN (increased renin due to focal compression of intrarenal arteries by cysts) (60-75%)
- \pm palpable kidneys

Common Complications

- urinary tract and cyst infections, HTN, CRF, nephrolithiasis (5-15%), flank and chronic back pain

Clinical Course

- polycystic changes are always bilateral and can present at any age
- clinical manifestations rare before age 20-25
- kidneys are normal at birth but may enlarge to 10 times normal size
- variable progression to renal functional impairment (ESRD in up to 50% by age 60)

Investigations

- radiographic diagnosis – best accomplished by renal U/S (enlarged kidneys, multiple cysts throughout renal parenchyma, increased cortical thickness, splaying of renal calyces)
- CT abdo with contrast (for equivocal cases, occasionally reveals more cystic involvement)
- gene linkage analysis for PKD1 for asymptomatic carriers
- Cr, BUN, urine R&M (to assess for hematuria)

Treatment

- goal: to preserve renal function by prevention and treatment of complications
- educate patient and family about disease, its manifestations and inheritance pattern
- genetic counselling: transmission rate 50% from affected parent
- prevention and early treatment of urinary tract and cyst infections (avoid instrumentation of GU tract)
- TMP/SMX, ciprofloxacin: able to penetrate cyst walls, achieve therapeutic levels
- adequate hydration to prevent stone formation
- avoid contact sports due to greater risk of injury to enlarged kidneys
- screen for cerebral aneurysms if family history of aneurysmal hemorrhages
- monitor blood pressure and treat hypertension with ACEI
- dialysis or transplant for ESRD (disease does not recur in transplanted kidney)
- may require nephrectomy to create room for renal transplant

Medullary Sponge Kidney

- common, autosomal dominant, usually diagnosed in 4th-5th decades
- multiple cystic dilatations in the collecting ducts of the medulla
- renal stones, hematuria and recurrent UTIs are common features
- an estimated 10% of patients who present with renal stones have medullary sponge kidney
- nephrocalcinosis on abdominal x-ray in 50% patients, often detect asymptomatic patients incidentally
- diagnosis: contrast filled medullary cysts on IVP, characteristic radial pattern ("bouquet of flowers"), "swiss cheese" appearance on morphology
- treat UTIs and stone formation as indicated
- does not result in renal failure

Autosomal Recessive Polycystic Kidney Disease

- 1:20,000 incidence
- prenatal diagnosis by enlarged kidneys
- perinatal death from respiratory failure
- patients who survive perinatal period develop CHF, HTN, chronic kidney disease
- treated with kidney and/or liver transplant

Common Medications

Table 14. Drugs In Nephrology

Classification	Examples	Site of Action	Mechanism of Action (Secondary Effect)	Indication	Dosing	Adverse Effects
Loop diuretics	furosemide (Lasix®) bumetanide (Bumex®/Buinec®) ethacrynate (Edecim®) torsemide (Demaex®)	Thick ascending of Loop of Henle	↓ Na/K/2Cl transport ± renal and peripheral vasodilatory effects (K loss; ↑ H secretion; ↑ Ca excretion)	Management of edema secondary to CHF; nephrotic syndrome, cirrhotic ascites; ↑ free water clearance (e.g. in SIADH-induced hyponatremia), ↓ BP (less effective due to short action)	furosemide: edema – 20-80 mg IV/IM/PO q6-8h (max 600 mg/d) until desired response HTN – 20-80 mg/d PO OD/bid dosing	Allergy in sulfa-sensitive individuals Electrolyte abnormalities: hypokalemia, hyponatremia, hypocalcemia, hypercalciuria (with stone formation) Volume depletion with metabolic alkalosis Precipitates gouty attacks
Thiazide Diuretics	hydrochlorothiazide (HCTZ) chlorthalidate (Diuril®) indapamide (Lozol®, Lozide®) metolazone (Zaroxolyn®) chlorthalidone (Hygroton®)	Distal convoluted tubule	Inhibit Na/Cl transporter (K loss; ↑ H secretion; ↓ Ca excretion)	1st line for essential HTN Treatment of edema Idiopathic hypercalciuria and stones Diabetes insipidus (nephrogenic)	HCTZ: edema – 25-100 mg PO OD HTN – 12.5-25 PO OD (max 50 mg/d) nephrolithiasis/hypercalciuria – 25-100 mg od	Hypokalemia Increased serum urate levels Precipitates gouty attacks, hypercalcemia Elevated lipids Glucose intolerance
Potassium-sparing	spironolactone (Aldactone®) triamterene (Dyrenium®) amilofide (Midamor®)	Cortical collecting duct (↓ Na reabsorption)	Aldosterone antagonist Closes apical Na channels directly	Reduces K loss caused by other diuretics Edema/hypervolemia Severe CHF, ascites (spironolactone), cystic fibrosis (amilofide ↓ viscosity of secretions)	spironolactone: 25-200 mg/day OD/bid dosing HTN: 50-200 mg/day OD/bid dosing Hyperaldosteronism – 100-400 mg/day OD/bid dosing amilofide: edema/HTN: 5-10 mg PO OD	Hypokalemia (caution with ACE inhibitor) Triamterene can be nephrotoxic (rare) Nephrolithiasis Gynecomastia (estrogenic effect of spironolactone)
Combination Agents	Dyazide® (triamterene + HCTZ) Aldactazide® (spironolactone + HCTZ) Moduretic® (amilofide + HCTZ) Vaseretic® (enalapril + HCTZ) Zestoretic® (lisinopril + HCTZ)		Combine ACE-inhibitor with thiazide for synergistic effect	Combine K-sparing drug with thiazide to reduce hypokalemia		
Osmotic Diuretics	mannitol (Osmitol®) glycerol urea	Renal tubules (proximal and collecting duct)	Non-reabsorbable solutes increase osmotic pressure of glomerular filtrate – inhibits reabsorption of water and ↑ urinary excretion of toxic materials	To ↓ intracranial or intraocular pressure Mobilization of excess fluid in renal failure or edematous states	mannitol: ↓ ICP: 0.25-2 g/kg IV over 30-60 min	Transient volume expansion Electrolyte abnormalities (↓/↑ Na, ↓/↑ K)
ACEI	ramipril (Altace®) enalapril (Vasotec®) lisinopril (Privil®) trandolapril (Mavik®) captopril (Capoten®)	Lungs Tissues diffusely	Prevents angiotensin II vasoconstricting vascular smooth muscle → net vasodilation → ↓ BP Prevents angiotensin II mediated aldosterone release from adrenal cortex and action on proximal renal tubules → ↑ Na and H ₂ O excretion → ↓ BP Reduces fibrosis and atherogenesis	HTN Cardioprotective effects (see Cardiology) Renoprotective effects	ramipril: HTN – 2.5-20 mg PO OD/bid dosing renoprotective use – 10 mg PO OD trandolapril: HTN – 1-4 mg PO OD	Cough Asthma Hyperkalemia Angioedema Agranulocytosis (captopril) Acute kidney injury Teratogenic
ARB	losartan (Cozaar®) candesartan (Atacand®) irbesartan (Avapro®) valsartan (Diovan®) telmisartan (Micardis®) eprosartan (Teveten®) olmesartan (Olmec®)	Vascular smooth muscle, adrenal cortex, proximal tubules	Competitive inhibitor at the angiotensin II receptor: prevents angiotensin II vasoconstricting action on vascular smooth muscle → ↓ BP Prevents angiotensin II mediated aldosterone release from adrenal cortex and action on proximal renal tubules → ↑ Na and H ₂ O excretion	HTN Cardioprotective effects (see Cardiology) Renoprotective effects	HTN: losartan 25-100 mg PO OD candesartan 8-32 mg PO OD irbesartan 150-300 mg PO OD valsartan 80-320 mg PO OD telmisartan 20-80 mg PO OD eprosartan 400-800 mg PO OD olmesartan 20-40 mg PO OD	Hyperkalemia Caution – reduce dose in hepatic impairment Acute kidney injury Teratogenic
Renin Antagonists	aliskiren (Rasilez®)	Direct renin antagonist	Inhibits renin production and activity Cardioprotective and renoprotective abilities being evaluated	HTN	aliskiren 150-300 mg PO OD	Hyperkalemia

Landmark Nephrology Trials

Trial	Reference	Results
ACEI and Diabetic	<i>NEJM</i> 1993; 329:1456-62	Captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy and is significantly more effective than blood-pressure control alone
BENEDICT	<i>NEJM</i> 2004; 351:1941-1951	Treatment with ACEI trandolapril alone or trandolapril combined with verapamil decreased the incidence of microalbuminuria in patients with type 2 diabetes and hypertension with normoalbuminuria
ASTRAL	<i>NEJM</i> 2009; 361:1953-62	Renal artery revascularization compared to medical therapy does not improve renal function, BP, renal or cardiovascular events, or mortality and carries significant operative risks
DETAIL	<i>NEJM</i> 2004; 351:1952-61	The ARB telmisartan and the ACEI enalapril are equally effective in slowing renal function deterioration in type 2 diabetes with mild to moderate hypertension and early nephropathy
ELITE	<i>NEJM</i> 2007; 257:2562-75	Standard immunosuppression therapy in renal transplant patients with low dose tacrolimus is superior to cyclosporine and sirolimus in reduction of acute rejection, maintenance of renal function, and allograft survival
HEMO	<i>NEJM</i> 2002; 347:2010-19	Use of high dose dialysis or high flux membranes versus standard dose or low flux in thrice-weekly dialysis does not improve survival or outcomes. Possible benefit in cardiac-related outcomes with high flux membranes
IDNT	<i>NEJM</i> 2001; 345:851-60	Treatment with irbesartan reduced the risk of developing end-stage renal disease and worsening renal function
IRMA	<i>NEJM</i> 2001; 345:870-8	Irbesartan is renoprotective independently of its blood-pressure lowering effect in patients with type 2 diabetes and microalbuminuria
ONTARGET	<i>Lancet</i> 2008; 372:547-33	Telmisartan and ramipril monotherapy reduced proteinuria and rise in creatinine in patients with high vascular risk
REIN	<i>Lancet</i> 1999; 354:359-64	In non-diabetic nephropathy, ACEI were renoprotective in patients with non-nephrotic range proteinuria
RENAAL	<i>NEJM</i> 2001; 345:861-9	Losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy and was generally well-tolerated
RENAL	<i>NEJM</i> 2009; 361:1627-38	High intensity continuous renal-replacement therapy in acute kidney injury does not improve survival or outcomes compared to low intensity treatment, and is associated with higher rates of hypophosphatemia
ROAD	<i>JASN</i> 2007; 18:1889-1898	Uptitration of either ACEI Benazepril or ARB Losartan to optimal anti-proteinuria doses conferred benefit on renal outcome in patients without diabetes and had proteinuria and renal insufficiency
SYMPHONY	<i>NEJM</i> 2007; 357:2562-75	Daclizumab induction, MMF, steroids and low-dose tacrolimus effectively maintain stable renal function following renal transplantation, without the negative effects on renal function commonly reported for standard CNI regimens

References

- Adler SG, Salant DJ. (2003). An outline of essential topics in glomerular pathophysiology, diagnosis and treatment for nephrology trainees. *American Journal of Kidney Diseases*, Vol. 42: 395-418.
- Andreoli TE et al. (2004). *Cecil Essentials of Medicine*, 6th ed., Saunders Publishing, Philadelphia.
- Androque HJ, Madias NM. (1999). Management of life threatening acid-base disorders part I. *NEJM*, Vol. 338 (1): 26-33.
- Androque HJ, Madias NM. (1999). Management of life threatening acid-base disorders part II. *NEJM*, Vol. 338 (2): 107-11.
- Androque HJ, Madias NE. (2000). Hyponatremia. *NEJM*, Vol. 342 (20): 1493-1499, 1581-1589.
- Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, et al. (2004). Angiotensin-Receptor Blockade versus Converting-Enzyme Inhibition in Type 2 Diabetes and Nephropathy. *NEJM*, Vol. 351(1): 1952-61.
- Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, et al. (2001). Effects of Losartan on Renal Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy. *NEJM*, Vol. 345(12): 861-869.
- Churchill DN, Blacke PG, Jindal KK, Toffelmire EB, Goldstein MB. (1999) Clinical practice guidelines for initiation of dialysis. *Canadian Society of Nephrology. J Am Soc Nephrol*; Vol. 10 (Suppl 13): S238-91.
- Donadio JV, Grande JP. (2002). Medical progress: IgA nephropathy. *NEJM*, Vol. 347: 738-748.
- Gabow PA. (1993). Autosomal dominant polycystic kidney disease. *NEJM*, Vol. 329(5):332-342.
- Greenberg, Arthur. *Primer on Kidney Diseases*, 3rd ed. San Diego: Academic Press, 2001.
- Hakim R, Lazarus M (1995). Initiation of Dialysis. *J Am Soc Nephrol*, Vol. 6, 1319-1328.
- Halperin ML, Goldstein MB, Kersey R, et al. (1998). Fluid, electrolyte, and acid-base physiology: a problem-based approach, 3rd ed. Harcourt Brace & Co.: New York.
- Halperin M, Kamel K. (1998). Potassium. *The Lancet*, Vol 352: 135-40.
- Harris SB, Meltzer SJ, Zinman B. (1998). New guidelines for the management of diabetes: a physician's guide. Steering Committee for the Revision of the Hemphill RR et al. Review of acute renal failure. <http://www.embs.com/cr/rt/rt.html>.
- Hudson BG, Tryggvason K, Sundaramoorthy M, Neilson EG. (2003). Mechanisms of Disease: Alport's Syndrome, Goodpasture's Syndrome, and Type IV Collagen. *NEJM*, Vol. 348: 2543-2556.
- Johnson CA, Levey AS, Coresh J, Levin A, Lau J, Eknoyan. G. (2004). Clinical practice guidelines for chronic kidney disease in adults: Part II. Glomerular filtration rate, proteinuria, and other markers. *American Family Physicians*, <http://www.aafp.org/afp/20040915/1091.html>
- Johnson RJ, Feehally J, eds (1999). *Comprehensive clinical nephrology*. Mosby: New York.
- K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification: 2000 executive update. <http://www.kidney.org/professionals/dogi/kdqi/toc.htm>
- Keane WF, Garabed E. (1999). Proteinuria, albuminuria, risk assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. *Amer J Kid Dis*, Vol. 33(5): 1004-1010.
- Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. (1993). The Effects of Angiotensin-Converting Enzyme Inhibition on Diabetic Nephropathy. *NEJM*, Vol. 329(20):1456-62.
- McFarlane P, Tobe S, Houlden R, Harris S. (2003). Nephropathy: Canadian Diabetes Association clinical practice guidelines expert committee. <http://www.diabetes.ca/cpg2003/downloads/nephropathy.pdf>.S66-S71.
- Meltzer, S et al. (1998). Clinical Practice Guidelines for the Management of Diabetes in Canada. *CMAJ*, 159(8):973-978.
- Myers, A. *Medicine* 4th ed. Baltimore: Lippincott Williams & Wilkins, 2001.
- ONTARGET Investigators. (2008) Telmisartan, ramipril, or both in patients at high risk for vascular events. *NEJM*, 358, 1547-59.
- Sabatine M. (2004). *Pocket Medicine: The Massachusetts General Hospital Handbook of Internal Medicine*. 2nd ed. Chapter 4, 1-20. New York. Lippincott Williams & Wilkins.
- Schiff H, Lang SM, Fischer R. (2002). Daily Hemodialysis and the Outcome of Acute Renal Failure. *NEJM*, Vol. 346(5):305-10.
- Schreiber M. Seminars for year 3 clinical clerks on medicine: hyponatremia and hypernatremia. October 29, 2002.
- Smith, Kinsey. *Renal Disease: A Conceptual Approach*. New York: Churchill Livingstone, 1987.
- Thadhani R, Pascual M, Bonventre JV. (1996). Acute renal failure. *NEJM*, Vol. 334(22):1448-1460.

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Anisocoria		Hemorrhagic Stroke	
Movement Disorders	25	Hypertensive Stroke	
Overview of Movement Disorders		Global Cerebral Ischemia	
Function of the Basal Ganglia		Treatment of Stroke	
Approach to Movements Disorders		Primary and Secondary Prevention	
Parkinson's Disease (PD)		Stroke Rehabilitation	
Other Parkinsonian Disorders		Multiple Sclerosis (MS)	49
Huntington's Disease		Common Medications	51
Dystonia		Landmark Neurology Trials	52
Tic Disorders		References	52
Tourette's Syndrome			
Motor Neuron Disease	29		
Amyotrophic Lateral Sclerosis (ALS)			
Other Motor Neuron Diseases			

The Neurological Exam



General Exam and Mental Status

- **vitals:** pulse (especially rhythm), BP, temperature
- **H&N:** meningismus, head injury/bruises (battle sign, raccoon eyes), tongue biting
- **CVS:** carotid bruits, heart murmurs

Neurological

- **mental status:** LOC (AVPU scale, Glasgow Coma Scale)
- **cognition:** Folstein Mini-Mental Status Exam (MMSE), clock drawing, frontal lobe testing (for perseveration)
 - clock drawing: give patient a blank piece of paper and tell them to draw the face of a clock, put in all the numbers, and set the hands to 'ten after eleven.'

Table 1. Mini-Mental Status Exam (MMSE)

Domain	Score	Task
Orientation	/5	Time: Year, Season, Month, Day, Date
	/5	Place: Country, Province, City, Building, Floor
Registration	/3	Immediate Recall: 3 unrelated items
Attention and Concentration	/5	Spell 'WORLD' backwards or do Serial 7s
Recall	/3	Delayed recall of previous 3 items
Language	/2	Naming: Pen, Watch
	/1	Repetition: 'No ifs, ands, or buts'
	/3	3-Step Command: "take this paper in your left hand, fold it in half, and place it on the floor with your right hand."
	/1	Read and obey: 'CLOSE YOUR EYES'
	/1	Writing: Write a full sentence
Drawing	/1	Copy: Intersecting Pentagons (10 angles, 2 bisecting)
TOTAL	/30	Cognitive impairment if <24/30



When testing CNII avoid noxious smells like ammonia as this tests CNV.



If patient has not brought their glasses, have them look through a pinhole for best corrected vision.



CNIII with pupil sparing – Think vascular causes like diabetic ophthalmoplegia
CNIII with pupil involvement – Think compressive lesions.



Caloric Reflexes

COWS
Cold
Opposite
Warm
Same



Contracting the left sternocleidomastoid turns the head right.



Tongue deviates to the weak side.

Cranial Nerves Exam

- **Olfactory (CNI):** test each nostril separately to identify common odours
- **Optic (CNII)**
 - a. Visual Acuity: test each eye individually using best corrected vision
 - b. Visual Fields: test all 4 quadrants for each eye individually
 - c. Pupil: direct and consensual pupillary reaction (afferent limb), accommodation, swinging flashlight test (for RAPD)
 - d. Fundoscopy: optic disc edema, optic disc pallor, venous pulsations, hemorrhages
- **Extra Ocular Movements (EOM)**
 - a. Oculomotor (CNIII): levator palpebrae superioris, medial rectus, superior rectus, inferior rectus, inferior oblique
 - b. Trochlear (CNIV): superior oblique
 - c. Abducens (CNVI): lateral rectus
- **Trigeminal (CNV)**
 - a. Sensory: V1-V3, corneal reflex (afferent)
 - b. Motor: temporalis, masseter, pterygoids, jaw jerk reflex
- **Facial (CNVII)**
 - a. Sensorimotor: muscles of facial expression, hyperacusis (stapedius), corneal reflex (efferent)
 - b. Visceral sensory: taste of anterior 2/3 of tongue
 - c. Visceral motor: salivary and lacrimal glands
- **Vestibulocochlear (CNVIII)**
 - a. Vestibular: nystagmus (described based on fast phase), caloric reflexes
 - b. Cochlear: test each ear masking the other with white noise, Rinne, Weber
- **Glossopharyngeal (CNIX) and Vagus (CNX):** palatal elevation, gag reflex, vocal cord function, swallowing
- **Accessory (CNXI):** trapezius and sternocleidomastoid
- **Hypoglossal (CNXII):** tongue muscle bulk, fasciculations, strength

Motor Exam

- **Bulk:** check symmetry for increased bulk or for atrophy
- **Abnormal movements:** tremors, chorea, dystonia, dyskinesia, hemiballism, myoclonus, athetosis, tic, fasciculations
- **Posture:** Parkinsonian, decerebrate, decorticate
- **Tone:** hypotonia (flaccid), hypertonia (spasticity, rigidity, paratonia), cogwheeling
- **Strength:** test strength at individual muscle groups, check pronator drift (see sidebar)
- **Reflexes:** deep tendon reflexes, abdominal reflexes, primitive reflexes, Babinski, Hoffman, clonus (see sidebar)

Table 2. Localization of Motor Deficits

	LMN	UMN	Extrapyramidal
Muscle Tone	Flaccid	Spastic	Rigid
Involuntary Movements	Fasciculations	None	Present (e.g., tremor)
Reflexes	Decreased	Increased	Normal
Babinski	Down-going	Up-going	Down-going
Weakness	Present	Present	Absent

Table 3. Overview of Neuromuscular Diseases

		Motor Neuron Disease	Peripheral Neuropathy	Neuromuscular Junction	Myopathy
S&S	Weakness	Segmental and asymmetrical, distal → proximal	Distal (except GBS) but may be asymmetrical	Proximal and fatiguable	Proximal
	Fasciculations	Yes	Yes	No	No
	Reflexes	Increased	Decreased/absent	Normal	Normal (until late)
	Sensory	No	Yes	No	No
	Autonomic*	No	Yes	No	No
Tests	EMG	Denervation and reinnervation	Signs of demyelination ± axonal loss	Decremental response Jitter on single fibre EMG	Small, short motor potentials
	NCS	Normal	Abnormal	Normal	Normal
	Muscle Enz	Normal	Normal	Normal	Increased

*e.g. orthostatic hypotension, anhydrosis, visual blurring, urinary hesitancy or incontinence, constipation, erectile dysfunction
Abbreviations: GBS – Guillain-Barré Syndrome

Table 4. Approach to Strength Testing of Radiculopathies versus Peripheral Neuropathies

How to use this table: For each nerve root, learn two (or more) peripheral nerves (and their associated muscles/movements). In radiculopathies, both peripheral nerves (and their movements) will be impaired. Whereas, in peripheral neuropathies, only one of the nerves (and its movement) will be impaired, sparing the other nerve. Especially useful peripheral nerve "pairs" are bolded for emphasis.

Root	Peripheral Nerve	Movement	Muscle
C5	Axillary	Shoulder abduction	Deltoid
C6	Musculocutaneous (C5, 6) Radial (C6)	Elbow flexion Elbow flexion Wrist extension	Biceps Brachioradialis Extensor carpi radialis longus
C7	Radial Posterior interosseus	Elbow extension Finger extension	Triceps Extensor digitorum communis
C8, T1	Median	Thumb flexion Thumb abduction Opposition	Flexor pollicis longus (look for thenar wasting) Abductor pollicis brevis (look for thenar wasting) Opponens pollicis (look for thenar wasting)
	Ulnar	Finger abduction	First dorsal interosseus (look for wasting in first dorsal webbed space)
L2, 3, 4	Femoral Obturator	Hip flexion Hip adduction	Iliopsoas Adductor muscles
L3, 4	Femoral (L3, 4) Deep peroneal (L4)	Knee extension Dorsiflexion	Quadriceps Tibialis anterior
L5	Sciatic (L5, S1) Tibial Superficial peroneal Deep peroneal	Hip extension Ankle inversion Ankle eversion Big toe extension	Gluteus maximus Tibialis posterior Peroneal muscles
S1	Sciatic Tibial	Knee flexion Plantarflexion	Hamstring muscles Gastrocnemius and soleus

MRC Muscle Strength Scale

- 5 Full power
- 4 Submaximal power against resistance (ranging 4+, 4, 4-)
- 3 Complete ROM without resistance
- 2 Complete ROM with gravity eliminated
- 1 Muscle flicker
- 0 No muscle contraction



Pyramidal Pattern of Muscle Weakness (i.e. UMN)

Arm extensors: shoulder abduction, elbow extension, wrist extension, finger extension, finger abduction

Leg flexors: hip flexion, knee flexion, ankle dorsiflexion



Primitive Reflexes

Grasp, palmomental, root, glabellar tap

Deep Tendon Reflexes

Root	Muscle Tendon
C5/6	Biceps
C6	Brachioradialis
C7	Triceps
C8	Finger Flexors
L2/3	Adductors
L3/4	Knee extensors
S1/2	Plantarflexion

Deep Tendon Reflex Scoring

0	Absent
1+	Depressed
2+	Normal
3+	Increased
4+	Clonus (≥4 beats)

Sensory Exam

- **primary sensation**
 - spinothalamic tract: pain and temperature
 - dorsal column: proprioception and vibration
- **cortical sensation**
 - graphesthesia, stereognosis, extinction, 2 point discrimination



Romberg

Stable with eyes open and closed = normal

Stable with eyes open, falls with eyes closed = +ve Romberg, suggesting loss of joint position sense

Falls with eyes open and closed = cerebellar or vestibular syndromes

Coordination Exam and Gait

- **coordination exam**
 - finger-to-nose, heel-to-shin, rapid alternating movement
- **stance and gait**
 - gait: ataxic, hemiplegic, ataxic, apraxic, festination, foot drop, broad-based
 - tandem gait
 - heel-to-toe walking
 - Romberg
 - pull test for retropulsion

Basic Anatomy Review

- see also Neurosurgery, NS24 for Dermatome/Myotome information

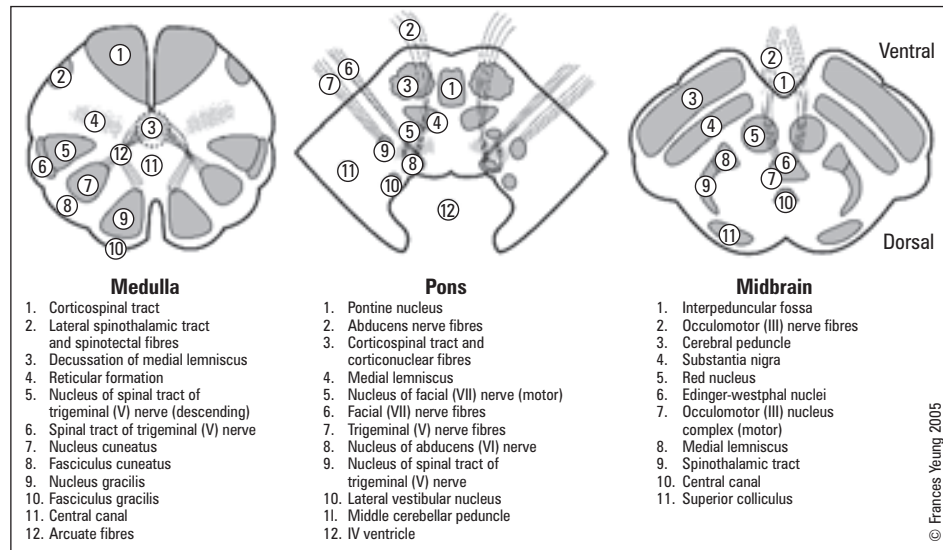


Figure 1. Brainstem

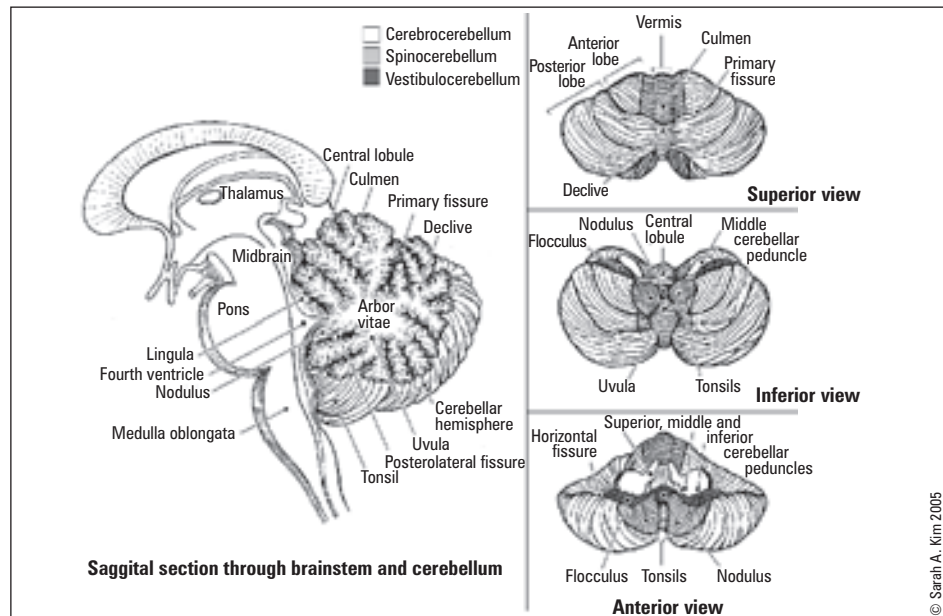


Figure 2. Cerebellum



See Functional Neuroanatomy software

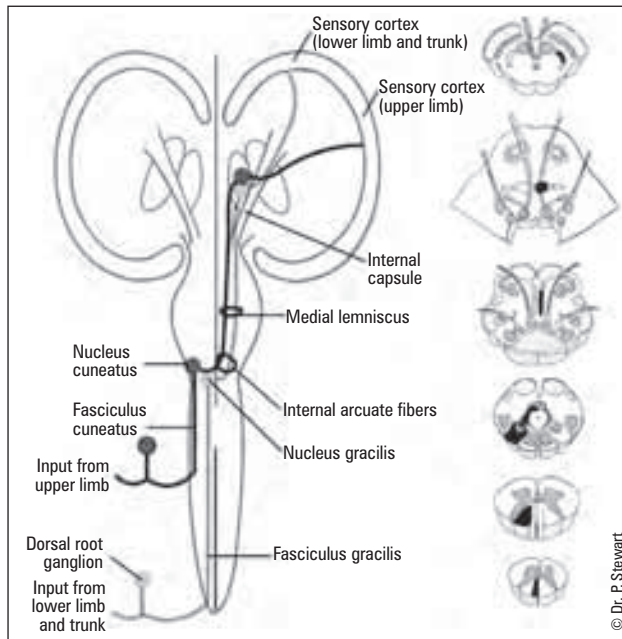


Figure 3. Discriminative Touch Pathway (Dorsal Column) from Body

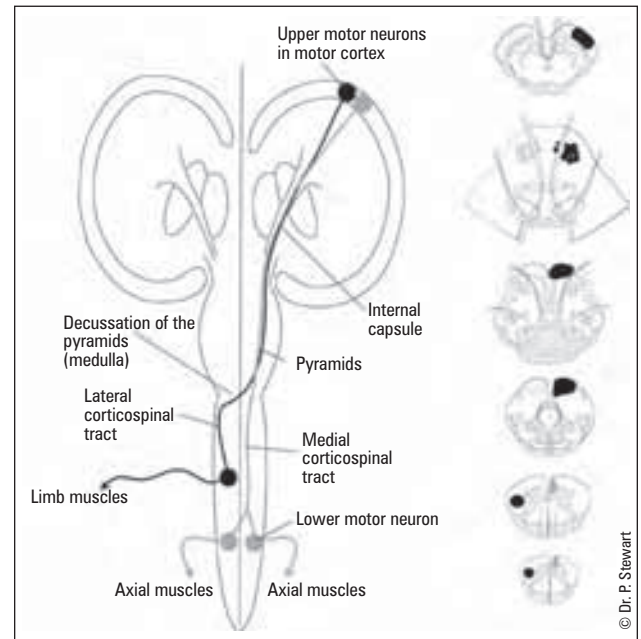


Figure 4. Spinothalamic Tract

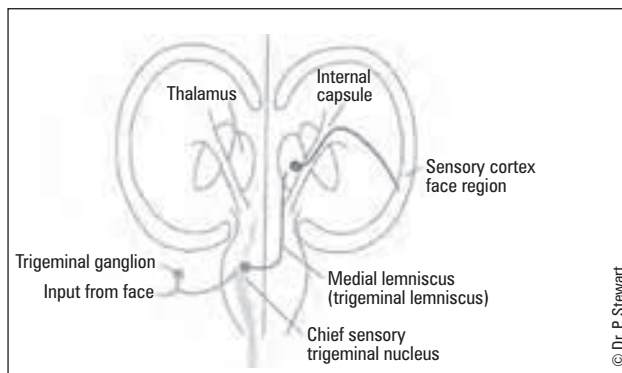


Figure 5. Discriminative Touch Pathway (Dorsal Column) from Face

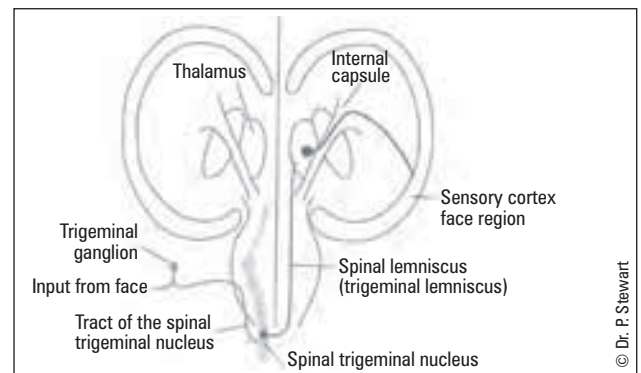


Figure 6. Spinothalamic Pain Pathway from Face

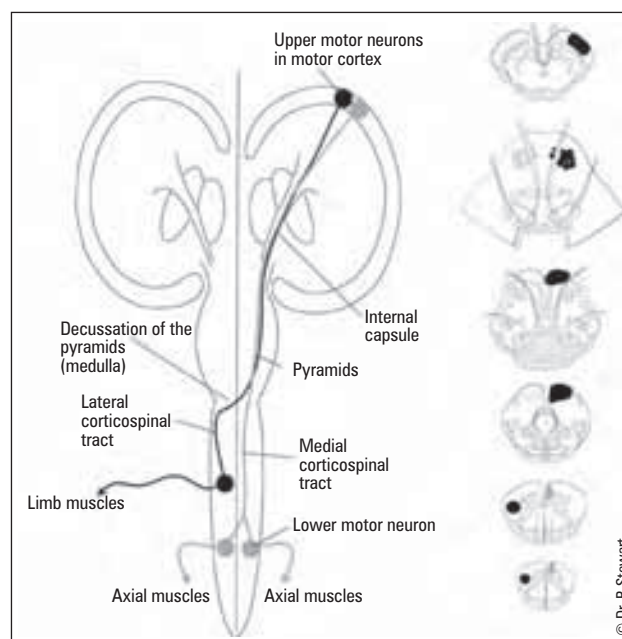


Figure 7. Corticospinal Motor Pathway

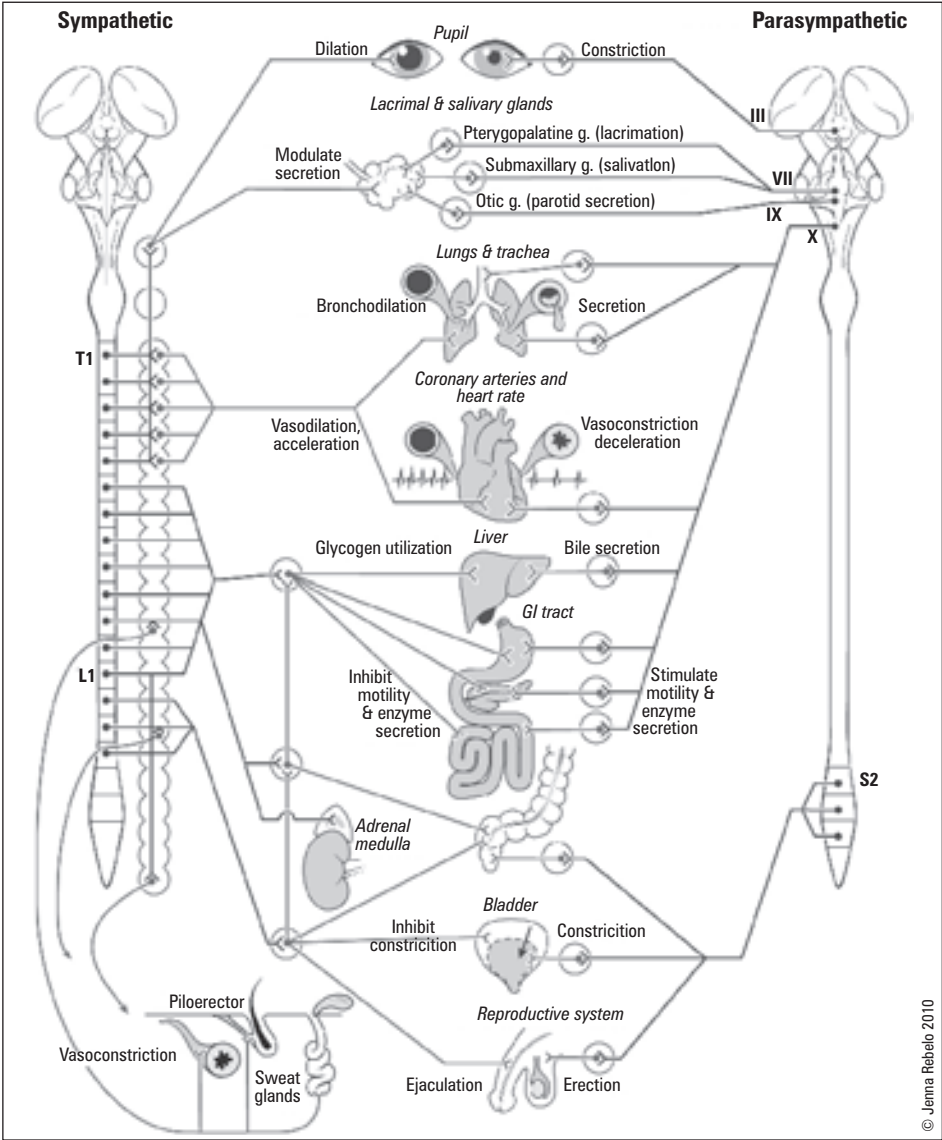


Figure 8. Sympathetic and Parasympathetic Pathway

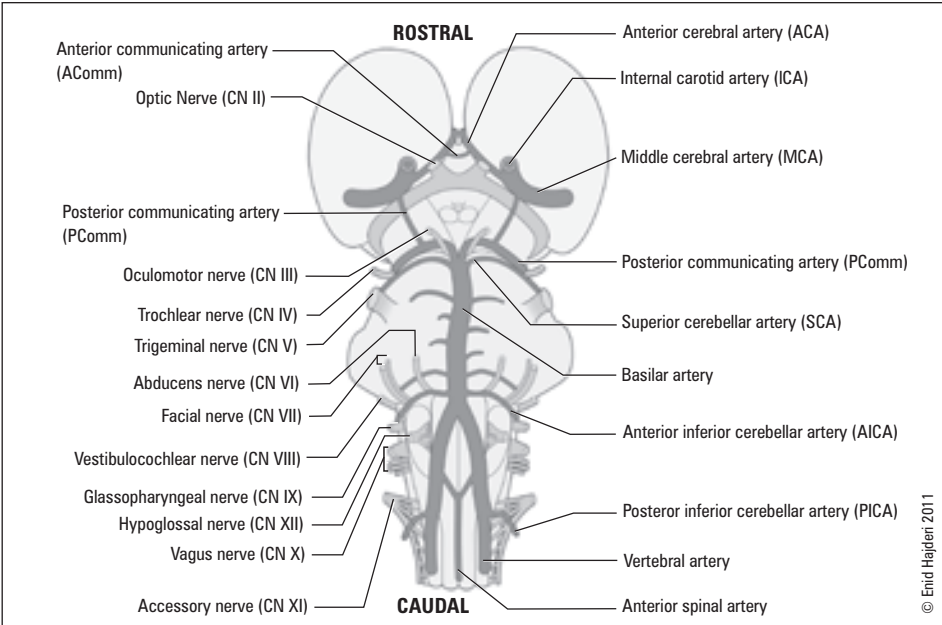


Figure 9. Brain Stem

Lumbar Puncture

Indications

- **diagnostic:** CNS infection (meningitis, encephalitis), inflammatory disorder (MS, Guillain-Barre, vasculitis), subarachnoid hemorrhage (CT negative), CNS neoplasm (neoplastic meningitis)
- **therapeutic:** to administer anesthesia, chemotherapy, contrast media; to decrease intracranial pressure (pseudotumour cerebri, normal pressure hydrocephalus)

Contraindications

- increased intracranial pressure (ICP) – could lead to cerebral herniation
 - CT first if immunocompromised, possible CNS disease, new-onset seizures, papilledema, altered LOC, focal neurologic findings, >60 years old
- infection over lumbar puncture (LP) site
- uncooperative patient

Complications

- tonsillar herniation
- post-LP headache (5-40%) – clear pattern: worse when upright, better supine; generally onset within 24 hrs
 - prevention: smaller gauge (i.e. 22) needle, reinsert stylet prior to needle removal, blunt ended needle
 - symptomatic treatment: caffeine and sodium benzoate injection
 - corrective treatment: blood patch
- spinal epidural hematoma
- infection

What to send LP for

- **Tube #1: Cell Count and Differential:** RBCs and WBCs and differential
 - xanthochromia [yellow bilirubin pigmentation] implies recent bleed into cerebrospinal fluid (CSF)
- **Tube #2: Chemistry:** Glucose (compare to serum glucose) and protein
- **Tube #3: Microbiology:** Gram stain and C&S
 - specific tests depending on clinical situation/suspicion
 - ♦ viral: PCR for herpes simplex virus (HSV)
 - ♦ bacterial: polysaccharide antigens of *H. influenzae*, *N. meningitidis*, *S. pneumococcus*
 - ♦ fungal: Cryptococcal antigen, India ink stain (cryptococcus), culture
 - ♦ TB: Acid-Fast stain, TB culture, TB PCR
- **Tube #4: Cytology** (for evidence of malignant cells)
- **Tube #5: RBCs:** compare RBC cell count to that of tube #1



The needle for a lumbar puncture is inserted into one of L3-4, L4-5, or L5-S1 interspaces.



The volume of CSF removed during a lumbar puncture is replenished within one hour.



Do not delay antibiotics while waiting for a lumbar puncture if suspicion of infection!



RBC in tube #1 > > #5 – traumatic tap
RBC in tube #1 = #5 – SAH

Table 5. Lumbar Puncture Interpretation (Normal vs. Various Infectious Causes)

Condition	Colour	Protein	Glucose	Cells
NORMAL	Clear	<0.45 g/l	60% of serum glc >3.0 mmol/l	0-5 WBC, 0 RBC 0 neutrophils
INFECTIOUS				
Viral Infection	Clear or opalescent	Normal or slightly increased <0.45-1 g/L	Normal	<1000x10 ⁶ /L Lymphocytes mostly, some PMNs
Bacterial Infection	Opalescent yellow, may clot	>1 g/L	Decreased (<25% serum glc or <2.0 mmol/L)	>1000x10 ⁶ /L PMNs
Granulomatous Infection (tuberculosis, fungal)	Clear or opalescent	Increased but usually <5 g/L	Decreased (usually <2.0-4.0 mmol/L)	<1000x10 ⁶ /L Lymphocytes



Seizure Disorders and Epilepsy

Seizure

Definitions

- **seizure** – transient neurological dysfunction caused by excessive activity of cortical neurons, resulting in paroxysmal alteration of behaviour and/or EEG changes
- **epilepsy** – chronic condition characterized by two or more unprovoked seizures
- **ictal** – during seizure
- **post-ictal** – period following a seizure when there may be a state of confusion/somnolence
- **inter-ictal** – period between seizures during which epileptic discharges may be seen on EEG
- **status epilepticus** – seizure lasting >30 minutes without spontaneous cessation or recurrent seizures without full return to consciousness inter-ictally

Classification

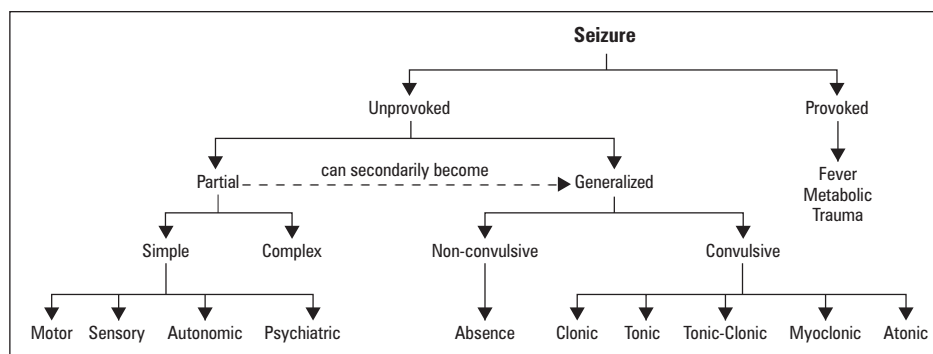


Figure 10. Classification of Seizures

Etiology

- idiopathic
- identifiable etiology: vascular, congenital, neurodegenerative or other neurologic disorders, neoplasm, trauma, childhood epilepsy syndromes, infection, metabolic, toxins, genetic
- cryptogenic

Signs and Symptoms

- **generalized seizures**
 - tonic-clonic (grand mal):
 - ♦ prodrome of unease or irritability hours to days before the attack
 - ♦ tonic ictal phase: tonic muscle contractions, arm flexion and adduction, leg extension, 'cry' as respiratory muscle spasm and air is expelled; lasts 10-30 seconds
 - ♦ clonic ictal phase: clonus involving violent jerking of face and limbs, tongue biting, incontinence; <90 seconds
 - ♦ post-ictal: decreased LOC, flaccid limb and jaw, extensor plantar reflexes, loss of corneal reflexes lasting hours, headache, confusion, aching muscles, sore tongue, amnesia, elevated serum CK lasting hours
 - absence (petit mal): usually only seen in children, unresponsive for 5-10 seconds with arrest of activity, staring, blinking or eye-rolling, no post-ictal confusion; 3Hz spike and slow wave activity on EEG
 - tonic: decreased LOC with muscle contraction in flexion or extension ± drop attack, arrest of respiration causing cyanosis
 - clonic: decreased LOC with repetitive clonic jerks
 - myoclonic: brief contractions localized to muscle groups of one or more extremities or more generalized
 - atonic: loss of postural tone leading to drop attack
- **partial seizures**
 - simple (no change in level of consciousness):
 - ♦ motor: rhythmic jerking or sustained spasm of localized muscles ± forceful turning of eyes and head to side contralateral to focal discharge (adversive seizure); may start in one location and spread to another (Jacksonian March); possible post-ictal hemiparesis (Todd's paralysis)
 - ♦ sensory: numbness/tingling/"electric" sensation of affected parts that may spread to other locations; other forms include visual, auditory, olfactory, gustatory, vertiginous
 - ♦ autonomic: epigastric discomfort, pallor, sweating, flushing, piloerection, papillary dilatation
 - ♦ psychiatric: symptoms rarely occur without impairment of consciousness and are more commonly complex partial



Medical Emergency! Status Epilepticus can cause irreversible brain damage without treatment.



Stroke is the most common cause of late-onset (>50 year of age) seizures, accounting for 50-80% of cases.

- complex (alteration of mood, memory, perception)
 - ♦ forms: dysphasic, dysmnestic (déjà vu), cognitive (disorientation of time sense), affective (fear, anger), illusions, structure hallucinations (music, scenes, taste, smells), epigastric fullness
 - ♦ automatism (chewing, swallowing, lip-smacking, scratching, fumbling, running, disrobing, continuation of actions prior to decreased LOC) followed by distant staring unresponsiveness

Table 6. Classic Factors Differentiating Seizure versus Syncope

Characteristic	Seizure	Syncope
Time of Onset	Day or night	Day
Position	Any	Upright, not recumbent
Onset	Sudden or brief	Gradual
Aura	Possible specific aura	Dizzy, blurring, lightheaded
Colour	Normal or cyanotic	Pallor
Autonomic	Uncommon outside of ictus	Common; diaphoresis
Duration	Brief or prolonged	Brief
Incontinence	Common	Possible but rare
Post-ictal	Occurs in tonic-clonic or complex partial	Rare
Motor Activity	Common	Occasional brief jerks
Injury	Common, tongue biting	Rare unless from fall
Automatisms	Common in absence or complex partial	None
EEG	Normal or Abnormal	Normal

Table 7. Classic Factors Differentiating Seizure versus Pseudoseizures (Conversion Disorder)

Characteristic	Seizure	Pseudoseizures*
Triggers	Uncommon	Emotional disturbance
Duration	Brief or prolonged	May be prolonged
Motor Activity	Synchronous, stereotypic, automatisms	Opisthotonos, rigidity, forced eye closure, irregular extremity movements, shaking head, pelvic thrust, crying
Timing	Day or Night	Day; other people present
Physical Injury	May occur	Rare
Incontinence	May occur	Rare
Reproduction of Attack	Spontaneous	Suggestion \pm stimulus
EEG	Often inter-ictal discharges	Normal
Prolactin	Increased	Normal

*Pseudoseizures do not rule out seizures (not uncommon to present with both)

Investigations

- evaluation of new onset seizures: history and physical, complete neurologic exam, CBC, electrolytes, FBG, calcium, magnesium, ESR, creatinine, urea, liver function tests, EEG, MRI (if suggestion of focal deficit, progression or >25 years of age)

Treatment

- anticonvulsants
- psychosocial issues: stigma of seizures, educate patient and family, advise of dangerous activities including driving, pregnancy issues
- surgical treatment if focal

Status Epilepticus

- initial measures: ABCs, vitals, ECG, nasal O₂, IV with NS, glucose 50 ml IV, thiamine 100 mg IV, EEG
- bloodwork: electrolytes, calcium, magnesium glucose, CBC, toxicology screen and alcohol level, anticonvulsant levels
- focused history
- general physical exam (once seizures controlled): LOC, vital signs, HEENT (tongue biting, papilledema), neck stiffness, signs of neurocutaneous disorders, decreased breath sounds, cardiac murmurs or arrhythmias, urinary incontinence, aphasia, motor exam



Complex partial status can resemble schizophrenia or psychotic depression.



Temporal lobe epilepsy is suggested by an aura of fear, olfactory or gustatory hallucinations; visceral, or déjà vu sensations.

Frontoparietal cortex seizures are suggested by contralateral focal sensory or motor phenomena.



Differential Diagnosis of Convulsions

Syncope, pseudoseizure, hyperventilation, panic disorder, TIA, hypoglycemia, movement disorder, alcoholic blackouts, migraines (confusional, vertebrobasilar), narcolepsy (cataplexy)



Note that frontal seizures (rare) can look like a pseudoseizure due to odd motor activity that may occur.



Pregnancy Issues

Teratogenicity of anticonvulsants due to increased risk of open neural tube defect. Advise patient planning pregnancy to take 5 mg/day of folic acid. Consider switching medications.



Ministry of Transportation must be contacted by law for all patients who have had a seizure. Patients will have license suspended until seizure free for 6 months.



Anticonvulsant Medications

Broad spectrum (generalized from onset and partial onset seizures): felbamate, lamotrigine, levetiracetam, rifampin, topiramate, valproate, zonisamide

Narrow spectrum (simple partial, complex partial and secondarily generalized seizures): carbamazepine, gabapentin, lacosamide, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, vigabatrin

Absence seizures (a type of generalized seizure): ethosuximide



Reflex asymmetry or unilateral Babinski sign may be indicative of a focal lesion.



EEG findings suggestive of Epilepsy: abnormal spikes, polyspike discharges, spike-wave complexes.



20-59% of first EEG are positive in epilepsy, 59-92% of epilepsy is picked up with repeated EEGs.

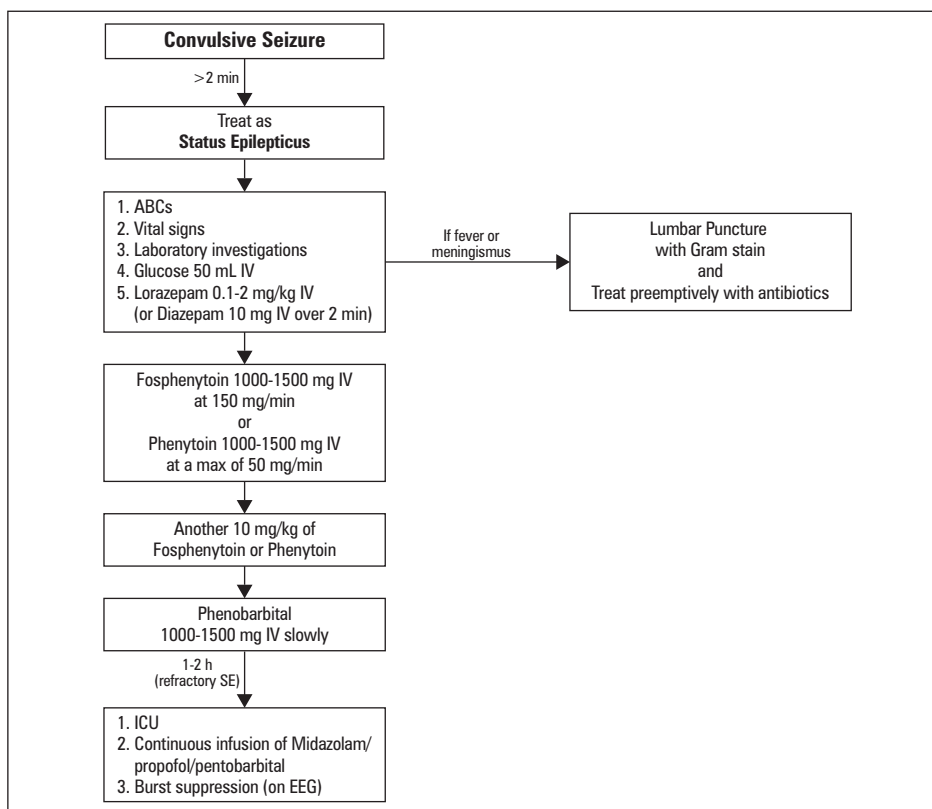


Figure 11. Status Epilepticus



Behavioural Neurology

- see [Psychiatry](#), PS17



Delirium is a medical emergency carrying significant risk of morbidity and mortality.



Delirium is characterized by acute onset, disorientation, marked variability, fluctuating level of consciousness, poor attention, and marked psychomotor changes.



Visual hallucinations more commonly indicate organic disease.



Etiology of Delirium
I WATCH DEATH
 Infectious
 Withdrawal from drugs
 Acute metabolic disorder
 Trauma
 CNS pathology
 Hypoxia
 Deficiencies in vitamins
 Endocrinopathies
 Acute vascular insults
 Toxins
 Heavy metals

Acute Confusional State/Delirium

Table 8. Selected Intracranial Causes of Acute Confusion

	Etiology	Key Clinical Features	Investigations
Vascular	Subarachnoid hemorrhage	Thunderclap headache Increased ICP Meningismus	CT (non-contrast) LP Angiography if CT, LP negative
	Stroke/TIA	Focal neurological signs	CT (non-contrast)
Infectious	Meningitis	Fever, headache, nausea, photophobia Meningismus	LP
	Encephalitis	Focal neurological signs Fever, headache, \pm seizure	LP; MRI
	Abscess	Increased ICP Focal neurological signs	CT with contrast (often ring enhancing lesion)
Traumatic	Diffuse axonal shear, epidural hematoma, subdural hematoma	Trauma Hx Increased ICP Focal neurological signs	CT (non-contrast) MRI
Autoimmune	Acute CNS vasculitis	Skin rash, active joints	ANA; ANCA; RF MRI Angiography
Neoplastic	Mass effect/edema, hemorrhage, seizure	Increased ICP Focal neurological signs Papilledema	CT (non-contrast) MRI
Seizure	Status epilepticus Todd's phenomenon	See <i>Seizure Disorders and Epilepsy</i> , N8	EEG
Primary Psychiatric	Psychotic disorder, mood disorder, anxiety disorder	No organic signs or symptoms	No specific tests

Management of Acute Confusion – General Measures

- see Psychiatry, PS18
- well-lit room
- hearing aids and glasses
- orienting stimuli (clocks, calendars)
- avoid restraints or catheters
- stop all unnecessary medications
- treat underlying cause, antipsychotics

Dementia

- see Psychiatry, PS18

Definition

- an acquired, generalized and (usually) progressive impairment of cognitive function (i.e. memory, recall, orientation, language, abstraction, etc.)
- affects content, but not level of consciousness

Epidemiology

- 15% of those >65 years of age have dementia
- common etiologies: 60-80% Alzheimer's Disease (AD); 10-20% vascular dementia
- <5% reversible: hypothyroid, normal pressure hydrocephalus (NPH), nutritional deficiencies, depression and infection

Etiology

- see Table 9 for common causes of dementia
- see Table 10 for acquired causes of dementia
- reversible causes: Wernicke-Korsakoff, medication (benzodiazepines, beta-blockers, anticholinergics), heavy metals, hepatic or renal failure, Wilson's Disease, B₁₂ deficiency, ↑/↓ glucose, ↑/↓ cortisol, thyroid dysfunction, NPH, depression (pseudodementia), brain tumour, subdural hematoma
- must rule out delirium

History

- geriatric giants
 - incontinence/falls/polypharmacy
 - memory and safety (wandering, leaving doors unlocked, leaving stove on, losing objects)
 - behavioural (mood, anxiety, psychosis, suicidal ideation, personality changes, aggression)
- ADLs and IADLs
- cardiovascular, endocrine, neoplastic, renal
- alcohol, smoking
- OTCs, herbal remedies, medications (sedative hypnotics, antipsychotics, antidepressants, anticholinergics), compliance, accessibility
- history of vascular disease, history of head trauma
- collateral history is usually very helpful

Physical Examination

- blood pressure
- hearing and vision
- neurological exam
- as directed depending on risk factors and history
- MMSE or MOCA
 - + clock drawing
 - + frontal lobe testing (go/no-go, word lists, similarities, proverb)
 - + Baycrest Neurocognitive Assessment

Investigations

- depends on suspected etiologies (see Tables 9 and 10)
 - CBC (note MCV for evidence of alcohol use), glucose, TSH, B₁₂, RBC folate
 - electrolytes, LFTs, renal function, lipids, serum calcium
 - CT head
 - MRI as indicated
 - as clinically indicated – VDRL, HIV, ANA, anti-dsDNA, ANCA, ceruloplasmin, copper, cortisol, toxicology, heavy metals
- issues to consider
 - failure to cope
 - fitness to drive
 - caregiver education and stress
 - ◆ respite services and day programs
 - power of attorney
 - wills
 - advanced directives (DNR)



ADLs "DEATH"	IADLs "SHAFT"
Dressing	Shopping
Eating	Housekeeping
Ambulating	Accounting
Toileting	Food preparation
Hygiene	Transportation



Vitamin B ₁₂ Deficiency Symptoms
• Macrocytic anemia
• Confusion or change in mental status (if advanced)
• Decreased vibration
• Distal numbness and paresthesia
• Weakness with UMN findings
• Diarrhea, anorexia, pallor, SOB
• Fatigue

**Dementia DDx****VITAMIN D VEST**

Vitamin deficiency (B₁₂, folate, thiamine)
 Intracranial tumour
 Trauma (head injury)
 Anoxia
 Metabolic (diabetes)
 Infection (postencephalitis, HIV)
 Normal pressure hydrocephalus
 Degenerative (Alzheimer's, Huntington's, CJD)
 Vascular (multi-infarct dementia)
 Endocrine (hypothyroid)
 Space occupying lesion (chronic subdural hematoma)
 Toxic (alcohol)

Table 9. Common Causes of Dementia

	Etiology	Key Clinical Features	Investigations
Primary Degenerative	Alzheimer's disease	Memory impairment Aphasia, apraxia, agnosia	CT or MRI, SPECT
	Lewy body disease	Hallucinations Parkinsonism Fluctuating cognition	CT or MRI, SPECT
	Frontotemporal dementia (e.g. Pick's disease)	Disinhibition, perseveration Decreased social awareness Progressive non-fluent aphasia Memory relatively spared	MRI, SPECT
Vascular	Huntington's disease	Chorea	Molecular testing
	Multi-infarct dementia	Abrupt onset Stepwise deterioration Dysexecutive syndrome Focal neurological findings	MRI, SPECT
	CNS vasculitis	Systemic S&S of vasculitis	ANA; ANCA; RF MRI Angiography

Table 10. Acquired Causes of Dementia

	Etiology	Key Clinical Features	Investigations
Infectious	Chronic meningitis	Fever, headache, nausea Meningismus Localizing neuro deficits	LP + investigations
	Chronic encephalitis	Fever, headache	LP; MRI
	Chronic abscess	Increased ICP Localizing neuro signs	CT with contrast
	HIV	See <u>Infectious Diseases</u> , ID29	HIV serology
	Creutzfeldt-Jacob disease	Rapidly progressive, myoclonus	EEG
	Syphilis	Ataxia, myoclonus	LP VDRL
Traumatic	Diffuse axonal shear, epidural hematoma, subdural hematoma	Trauma Hx Increased ICP, papilledema Localizing neuro signs	CT (non-contrast)
Rheumatologic	SLE	See <u>Rheumatology</u> , RH9	MRI; ANA, anti-dsDNA
Neoplastic	Mass effect/edema, hemorrhage, seizure	Increased ICP Localizing neuro signs	CT with contrast MRI
	Paraneoplastic encephalitis	Systemic S&S of cancer	Anti-Hu antibodies

Alzheimer's Disease (AD)

- see Psychiatry, PS18

Definition

- progressive cognitive decline interfering with social and occupational functioning characterized by the following
 1. anterograde amnesia – impaired ability to learn new information
 2. one of the following cognitive disturbance
 - a. Aphasia – language disturbance
 - b. Apraxia – impaired ability to carry out motor activities despite intact motor function
 - c. Agnosia – failure to recognize or identify objects despite intact sensory function
 - d. Disturbance in executive function – planning, organizing, sequencing, abstracting

Pathophysiology

- genetic factors
 - a minority (<7%) of AD cases are familial, autosomal dominant
 - 3 major genes for autosomal dominant AD have been identified:
 - ♦ amyloid precursor protein (chromosome 21)
 - ♦ presenilin 1 (chromosome 14)
 - ♦ presenilin 2 (chromosome 1)
 - the E4 polymorphism of apolipoprotein E is a susceptibility genotype (E2 is protective)

**4 A's and one D of AD**

Anterograde amnesia
 Aphasia
 Apraxia
 Agnosia
 Disturbance in executive function

- pathology (although not necessarily specific for AD)
 - gross pathology
 - ♦ diffuse cortical atrophy, especially frontal, parietal, and temporal lobes
 - microscopic pathology
 - ♦ senile plaques (extracellular deposits of amyloid in the gray matter of the brain)
 - ♦ neurofibrillary tangles (intracytoplasmic paired helical filaments with beta-amyloid and hyperphosphorylated Tau protein)
 - biochemical pathology
 - ♦ 50-90% reduction in action of choline acetyltransferase

Epidemiology

- 1/12 of population 65-75 years of age
- 1/3 of population >85 years of age
- accounts for 60-80% of all dementias

Risk Factors

- family history of AD
- head injury
- low education level
- smoking
- aluminum (controversial)
- Down's syndrome

Signs and Symptoms

- cognitive impairment
 - memory impairment for newly acquired information (early)
 - deficits in language, abstract reasoning, and executive function
- psychiatric manifestations
 - major depressive disorder (5-8%)
 - psychosis (20%)
- motor manifestations (late)
 - parkinsonism (consider Lewy body disease)

Investigations

- perform investigations to rule out other causes of dementia as necessary
- EEG: generalized slowing (nonspecific)
- MRI: dilatation of lateral ventricles; widening of cortical sulci
- SPECT: hypometabolism in temporal and parietal lobes

Treatment

- acetylcholinesterase inhibitors have been shown to improve cognitive function
 - donepezil (Aricept®), rivastigmine (Exelon®), galantamine (Reminyl®)
 - relative contraindications: bradycardia, arrhythmia, CHF, CAD, asthma, COPD, ulcers, or increased risk of ulcers and GI bleeding
 - galantamine is contraindicated in patients with hepatic/renal impairment
- memantine (Ebixa®) is an NMDA-receptor antagonist that has some benefits in later stage AD
- other – although efficacy not proven
 - ginkgo biloba
 - Vit E (caution: >400 IU/day associated with excess mortality, level 1 evidence)
- symptomatic management
 - low dose neuroleptic
 - trazodone for sleep disturbance
 - antidepressants

Prognosis

- progressive
- mean duration of disease 10 years

Lewy Body Disease (LBD)

Definition

- progressive cognitive decline interfering with social or occupational function; memory loss may or may not be an early feature
- one (possible LBD) or two (probable LBD) of the following:
 - fluctuating cognition with pronounced variation in attention and alertness
 - recurrent visual hallucinations
 - parkinsonism

Etiology and Pathogenesis

- Lewy bodies (eosinophilic cytoplasmic inclusions) found in both cortical and subcortical structures

Epidemiology

- 15-25% of all dementias

Signs and Symptoms

- fluctuation in cognition with progressive decline
- visual hallucinations
- parkinsonism
- repeated falls
- sensitivity to neuroleptic medications (develop rigidity, neuroleptic malignant syndrome, extrapyramidal symptoms)
- REM sleep disorder

Treatment

- acetylcholinesterase inhibitors (e.g. donepezil)

Prognosis

- typical survival 3-6 years

Frontotemporal Dementia (FTD)

Definition

- progressive dementia characterized by core symptoms of either disinhibition and emotional lability or of apathy and detachment

Etiology and Pathogenesis

- gross pathology
 - atrophy of frontal and temporal poles
- microscopic pathology
 - Pick bodies (intraneuronal inclusions containing abnormal Tau proteins)

Epidemiology

- 10% of all dementias

Signs and Symptoms

- core features
- behavioural disorder
 - impairment of personal conduct and of regulation of social interactions
 - decline in personal hygiene and grooming
 - mental rigidity/inflexibility
 - perseverative and stereotyped behaviour
- speech and language
 - altered speech output (economy or pressure of speech)
 - echolalia/perseveration
- physical signs
 - primitive reflexes (i.e. pout, grasp, palmomental, glabellar)
 - parkinsonism

Investigations

- MRI/SPECT – frontotemporal atrophy/hypometabolism

Creutzfeldt-Jakob Disease (CJD)

Definition

- rare degenerative fatal brain disorder

Pathophysiology

- prion proteins causing alterations in the brain such as spongiform changes, astrogliosis and neuronal loss

Epidemiology

- rare (1 in a million), peak incidence between 50-70 years old

Clinical Presentation

- sporadic CJD: rapidly progressive dementing illness causing death within months, associated with myoclonus
 - cerebellar ataxia
 - extrapyramidal signs
 - akinetic mutism and cortical blindness sometimes occur
 - fatal within 1 year
 - EEG: triphasic complexes

Diagnosis

- rule out treatable dementia, neurologic exam, EEG, MRI
- only way to confirm diagnosis is brain biopsy/autopsy

Types

- sporadic CJD: most common form (85%), no risk factors
- hereditary CJD: family history or tests positive for genetic mutation (5-10%)
- acquired CJD: transmitted via exposure to prion in nervous system tissue (<1%)
 - iatrogenic CJD transmitted in organ transplants, injections (human growth hormone products), electrodes
- variant: earlier onset, more psychiatric symptoms, longer duration, absence of triphasic complexes on EEG (i.e. Mad Cow disease)
- kuru: historically due to cannibalism in Papua New Guinea
- panencephalopathic form: primarily seen in Japan, progresses over years

Histopathology

- spongiform changes, astrocytosis and neuronal loss
- occur sporadically

Treatment

- no known treatment



Prion proteins have a normal form and an infectious form. The infectious form is abnormally folded and leads to abnormal folding of normal prion proteins. These abnormally folded proteins aggregate leading to neuronal loss.

Normal Pressure Hydrocephalus

- see Neurosurgery, NS7



NPH Progression of Classic Triad

AID
Ataxia/Apraxia of Gait → Incontinence
→ Dementia

Aphasia

Definition

- an acquired disturbance of language characterized by errors in speech production, writing, comprehension, or reading

Neuroanatomy of Aphasia

- Broca's area (posterior inferior frontal lobe) involved in speech production (expressive)
- Wernicke's area (posterior superior temporal lobe) used for comprehension of language (receptive)
- angular gyrus is responsible for relaying written visual stimuli to Wernicke's area for reading comprehension
- the arcuate fasciculus association bundle connects Wernicke's and Broca's areas
- >99% of right-handed people have left hemisphere language representation
- 70% of left-handed people have left hemisphere language representation, 15% have right hemisphere representation, and 15% have bilateral representation

Assessment of Language

- assessment of context
 - handedness (writing, drawing, toothbrush, scissors)
 - education level
 - native language
 - learning difficulties
- assessment for aphasia
 1. spontaneous speech
 - ♦ fluency
 - ♦ paraphasias: semantic ("chair" for "table"), or phonemic ("clable" for "table")
 2. repetition
 3. naming
 4. comprehension (auditory and reading)
 5. writing
 6. neologisms



The left hemisphere is dominant for language in almost all right-handed people and 70% of left-handed people.

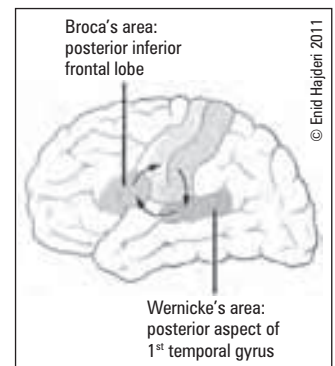


Figure 12. Broca's and Wernicke's Areas



Aphasia localizes the lesion to the dominant cerebral hemisphere.

Table 11. Approach to Aphasias

	Fluency	Comprehension	Repetition	Naming	Lesion Localization
Broca's	Non-fluent	Good	Poor	Poor	Posterior inferior frontal lobe
Motor TCA*	Non-fluent	Good	Good	Poor	1. Frontal lobe watershed between MCA and ACA territories 2. White matter lesions deep to (1)
Mixed TCA*	Non-fluent	Poor	Good	Poor	Combined sensory and motor transcortical
Global	Non-fluent	Poor	Poor		Posterior inferior frontal lobe AND posterior superior temporal lobe
Wernicke's	Fluent	Poor	Poor	Relatively Spared	Posterior superior temporal lobe
Conduction	Fluent	Good	Poor	Poor	Arcuate fasciculus
Sensory TCA*	Fluent	Poor	Good	Relatively Spared	1. Subcortical temporoparietal 2. Temporoparietal watershed between MCA and PCA territories
Anomic	Fluent	Good	Good	Poor	Numerous possible locations

TCA=Transcortical aphasia

*Transcortical aphasias are typically associated with cerebral anoxia (e.g. post-MI, CO poisoning, hypotension)

Prognosis

- most recovery from stroke-related aphasia occurs in first three months, but may continue for >1 year
- with recovery, the type of aphasia may evolve
- poor prognosis: global aphasia

Apraxia

Definition

- inability to perform skilled voluntary motor sequences that cannot be accounted for by weakness, ataxia, sensory loss, impaired comprehension, or inattention

Clinicopathological Correlations

Table 12. Apraxia

	Description	Tests	Hemispheres
Ideomotor	Inability to perform skilled learned motor sequences	Blowing out a match; combing one's hair	Left
Ideational	Inability to sequence actions	Preparing and mailing an envelope	Right and left
Constructional*	Inability to draw or construct	Copying a figure	Right and left
Dressing*	Inability to dress	Dressing	Right

* Refers specifically to the inability to carry out the learned movements involved in construction, drawing, or dressing; not merely the inability to construct, draw, or dress. Many skills aside from praxis are needed to carry out these tasks.

Agnosia

Definition

- disorder in the recognition of the significance of sensory stimuli in the presence of intact sensation and naming

Clinicopathological Correlations

Table 13. Agnosias

	Description	Lesion
Aperceptive Visual Agnosia	Inability to name or demonstrate the use of an object presented visually 2° to distorted visual perception Recognition by touch remains intact	Bilateral temporo-occipital cortex
Associative Visual Agnosia	Inability to name an object presented visually 2° to disconnect between visual cortex and language areas Visual perception is intact as demonstrated by visual matching	Bilateral inferior temporo-occipital junction
Prosopagnosia	Inability to recognize familiar faces in the presence of intact visual perception and intact auditory recognition	Bilateral occipitotemporal areas or right inferior temporo-occipital region
Colour Agnosia	Inability to perceive colour	Bilateral inferior temporo-occipital lesions
Astereognosis	Inability to identify objects by touch	Anterior parietal lobe in the hemisphere opposite the affected hand
Finger Agnosia	Inability to recognize, name, and point to individual fingers	Dominant hemisphere parietal-occipital lesions



Parietal Lobe Lesions

Lesions of the dominant parietal lobe are characterized by Gerstmann's Syndrome: acalculia, agraphia, finger agnosia, and left-right disorientation. Lesions of the non-dominant parietal lobe are characterized by neglect, anosognosia, and cortical sensory loss.

Cranial Nerve Deficits

CN I: Anosmia

Clinical Features

- absence of sense of smell associated with a loss of taste
- usually not recognized by patient if it is unilateral

Classification

- **nasal:** odours do not reach olfactory receptors because of physical obstruction
 - heavy smoking, chronic rhinitis, sinusitis
- **olfactory neuroepithelial:** destruction of receptors or their axon filaments
 - influenza, herpes simplex, interferon treatment of hepatitis C virus, atrophic rhinitis (leprosy)
- **central:** lesion of olfactory pathway
 - Kallman syndrome, albinism, head injury, cranial surgery, SAH, chronic meningeal inflammation, meningioma, aneurysm, Parkinson's disease



If anosmia is not associated with loss of taste, consider malingering.



Kallmann's syndrome is a congenital disorder of anosmia and hypogonadotropic hypogonadism.

CN II: Optic Nerve

- see *Neuro-Ophthalmology*, N20

CN III: Oculomotor Nerve

Clinical Features

- ptosis, resting eye position is "down and out" (depressed and abducted), pupil dilated (mydriasis)

Common Lesions

- midbrain: bilateral with contralateral pyramidal signs ± mydriasis
- posterior communicating artery aneurysm: early mydriasis then CNIII palsy
- cavernous sinus (internal carotid aneurysm, meningioma, sinus thrombosis)
- ischemia of CNIII (DM, temporal arteritis, HTN, atherosclerosis): pupil sparing



Pupillary constrictor fibres are on the peripheral aspect of CNIII so compression of the nerve leads to mydriasis while infarction (affecting centre of nerve) causes pupillary sparing.



Lesions involving the cavernous sinus lead to cranial nerve palsies of III, IV, VI, V1 and V2 as well as pain and proptosis.

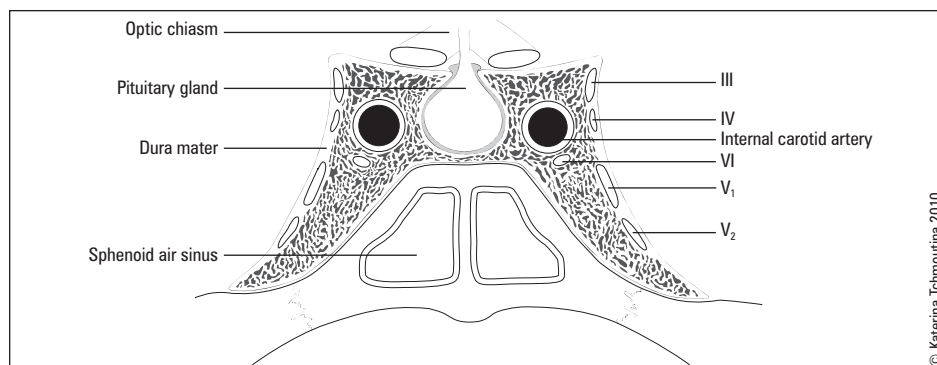


Figure 14. Cavernous Sinus

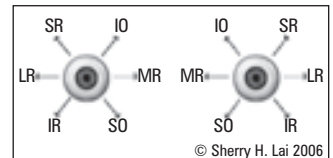


Figure 13. Diagnostic Positions of Gaze to Isolate Primary Action of Each Muscle



CN IV is the only cranial nerve that exits posteriorly and crosses the midline. A CN IV lesion may cause a contralateral deficit.



CN IV is at risk of trauma during neurosurgical procedures involving the midbrain because of its long intracranial course.



Herpes Zoster of Trigeminal Nerve: typically involves V1 (ophthalmic division).

Hutchinson's Sign: tip of nose involvement; predicts corneal involvement.



CN VI has the longest intracranial course and is vulnerable to increased ICP, creating a false localizing sign.



Forehead is spared in a UMN CN VII lesion due to bilateral innervation from cerebral hemispheres.

CN IV: Trochlear Nerve

Clinical Features

- diplopia (with downward and inward gaze), minimized with head tilt to opposite side
- patient may complain of difficulty going down stairs or reading

Lesions

- common: ischemic (DM, HTN), idiopathic, trauma (TBI or surgical), congenital
- other: cavernous sinus lesion, orbital fissure (tumour, granuloma)

CN V: Trigeminal Nerve

Lesions

- trigeminal neuralgia, herpes zoster, cavernous sinus, orbital fissure, trauma, cerebellopontine angle tumours, demyelination, syringobulbia, metastatic infiltration of nerve, ipsilateral brainstem lesion, contralateral parietal lesion

Trigeminal Neuralgia (Tic Douloureux)

- excruciating unilateral paroxysmal shooting "electric" pains in trigeminal root territory
 - usually in V3 distribution \pm V₁, V₂
 - normal sensory exam
- etiologies: idiopathic, compression by tortuous blood vessel (SCA), cerebellopontine angle tumour (5%), multiple sclerosis (5%)
- pain lasts seconds/minutes over days/weeks; remits for weeks/months
- triggers: touching face, eating, talking, cold wind, shaving, applying make-up
- F > M; usually middle-aged and elderly
- medical treatment: carbamazepine; narcotics do not help
- if medical treatment fails (order increasingly invasive): gamma knife, invasive percutaneous denervation (radiofrequency/glycerol), percutaneous balloon microcompression, microvascular decompression
- rule out structural lesion, multiple sclerosis or vascular lesion with MRI

CN VI: Abducens Nerve

Clinical Features

- inability to abduct the eye on the affected side
- patient complains of horizontal diplopia, worse on ipsilateral lateral gaze

Common Lesions

- pons (infarction, hemorrhage, demyelination) – associated with facial weakness and contralateral pyramidal signs
- tentorial orifice (compression, meningioma) – false localizing sign of increased ICP
- cavernous sinus (carotid aneurysm, thrombosis)
- vascular – may be secondary to DM, HTN, or temporal arteritis
- congenital – Duane's syndrome

CN VII: Facial Nerve

Clinical Features

- ipsilateral facial weakness (involuntary and voluntary)
- impaired lacrimation, decreased salivation, numbness behind auricle, hyperacusis, taste dysfunction of anterior 2/3 of tongue

Investigations

- brainstem (LMN) versus cortical (UMN) symptoms and signs help localize lesion

Differential Diagnosis

- idiopathic = Bell's Palsy, 80-90% of cases (see Otolaryngology, OT23)
- other: temporal bone fracture, EBV, Ramsay-Hunt (HSV), otitis media/mastoiditis, sarcoidosis, DM mononeuropathy, parotid gland disease

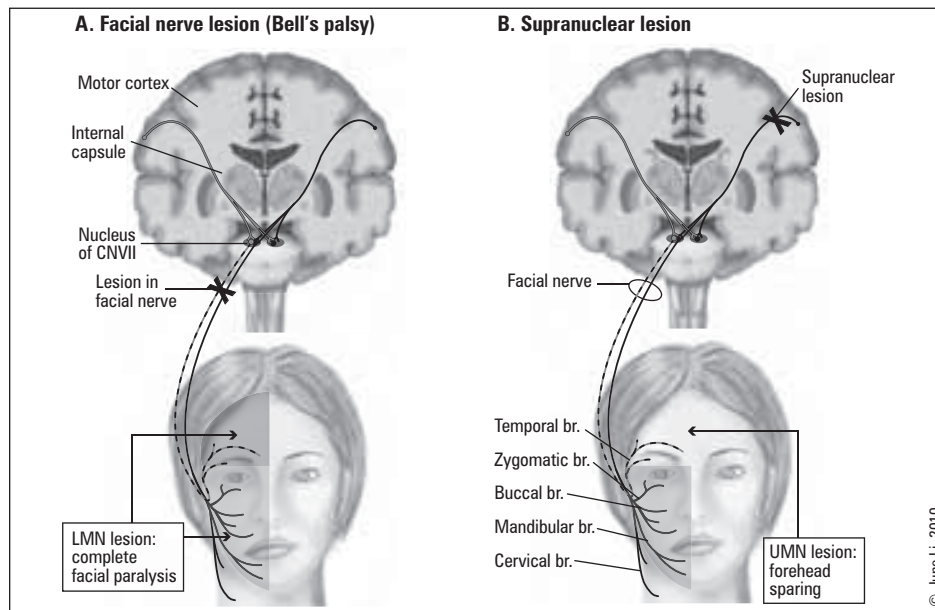


Figure 15. UMN vs. LMN Facial Nerve Palsy

CN VIII: Vestibulocochlear Nerve

- see Otolaryngology, OT12

CN IX: Glossopharyngeal Nerve

Clinical Features

- sharp paroxysmal pain of posterior pharynx radiating to ear, triggered by swallowing
- taste dysfunction in posterior 1/3 of tongue
- absent gag reflex (dysphagia)

Treatment

- carbamazepine or surgical ablation of CN IX

CN X: Vagus Nerve

Clinical Features

- dysphagia (palatal and pharyngeal weakness)
- dysarthria (laryngeal weakness): inability to produce understandable speech due to impaired phonation (laryngeal sound production) and/or resonance (the alteration of sounds in the cavity between the larynx and the lips/nares) secondary to impaired motor control over peripheral speech organs

Table 14. Classification of Dysarthria

Classification	Characteristics of Speech	Etiologies*
Flaccid (LMN dysarthria or bulbar palsy)	Slurred, indistinct speech Particular difficulty with vibratory "R" Difficulty with lingual consonants produced by tongue and labial consonants produced by lips	Motor neuron (e.g. ALS) Peripheral nerve (e.g. GBS) Neuromuscular junction (e.g. MG) Myopathy (e.g. DM/PM)
Spastic UMN (dysarthria or pseudobulbar palsy)	Slow and monotonous Strained or strangled Harsh Low pitched	Stroke Tumour Demyelination Degeneration
Ataxic	Slow/alterd rhythm Improper stress	Cerebellar disease Cerebellar outflow tract disease



When screening for the presence of dysphagia and assessing risk for aspiration, the presence of a gag reflex is insufficient. Rather, the correct screening test is to observe the patient drinking water from a cup and looking for coughing, choking, or "wetness" of voice.



Differential Diagnosis of Lower Cranial Nerve deficits (CN IX, X, XI, XII)
Intracranial/skull base: meningioma, neurofibroma, metastases, osteomyelitis, meningitis
Brainstem: stroke, demyelination, syringobulbia, poliomyelitis, astrocytoma
Neck: trauma, surgery, tumours



Normal swallowing is initiated when the tongue throws a bolus back into the palatal archway – tongue movements are innervated exclusively by CN XII. The bolus stimulates the soft palate to elevate and the bolus is deflected into the oropharynx. Next the pharyngeal constrictors contract, the larynx elevates, and the vocal cords close. Swallowing depends on afferent information via CN V, IX, and X and motor action via CN V, VII, IX, X, and XII.

Connections in the nucleus of the tractus solitarius in the medulla, in proximity to the respiratory centre, act as the swallowing centre. Swallowing and breathing are coordinated to prevent aspiration.

Table 14. Classification of Dysarthria (continued)

Classification		Characteristics of Speech	Etiologies*
Extrapyramidal	Hypokinetic	Low-pitched Monotonous Decrescendo volume	Parkinson's disease Other causes of parkinsonism (see <i>Movement Disorders</i>)
	Hyperkinetic	Choreiform • Prolonged sentence segments intermixed with silences • Variable, improper stress • Bursting quality Dystonic • Slow speaking rate • Prolonged individual phonemes	Huntington's disease Dystonia musculorum deformans Other hyperkinetic extrapyramidal disorders (see <i>Movement Disorders</i>)

*Abbreviations: ALS – amyotrophic lateral sclerosis; GBS – Guillain-Barré syndrome; MG – myasthenia gravis; DM – dermatomyositis; PM – polymyositis



CN XI is vulnerable to damage during neck surgery.

CN XI: Accessory Nerve

Clinical Features

- ipsilateral shoulder drop, weakness on turning head to contralateral side

CN XII: Hypoglossal Nerve

Clinical Features

- tongue deviation toward side of lesion
- chronic LMN lesion: ipsilateral tongue atrophy and fasciculations

NEURO-OPHTHALMOLOGY

Abnormalities of Vision



Acute Visual Loss

- **ophthalmologic:** acute angle closure glaucoma, vitreous hemorrhage, retinal detachment
- **optic nerve:** optic neuritis, anterior ischemic optic neuropathy (arteritic, non-arteritic), compression by space occupying lesion (e.g. aneurysm)
- **vascular:** TIA/amaurosis fugax, central retinal artery or vein occlusion, carotid-cavernous sinus fistula
- **CNS:** stroke, optic tract/chiasm lesion, migraine
- **infection/inflammation:** endophthalmitis

Optic Neuritis

- see *Optic Disc Edema*, N21, *Multiple Sclerosis*, N49

Anterior Ischemic Optic Neuropathy

- see also *Optic Disc Edema*, N21
- **clinical presentation:** painless vision loss over hours to days
- **non-arteritic (NAION):** vision loss due to atherosclerosis
- **arteritic (AION):** normally due to giant cell arteritis (see *Rheumatology*, RH17)

Amaurosis Fugax

- see *Ophthalmology*, OP37 and *Stroke* section, N44

Central Retinal Vein Occlusion (CRVO)

- see *Ophthalmology*, OP24



If you suspect the diagnosis of giant cell arteritis do not wait for biopsy results. Begin treatment immediately!

Optic Disc Edema

Table 15. Common Causes of Optic Disc Edema

	Optic Neuritis	Papilledema	AION	CRVO
Age	<50	Any	>50	>50
Vision	Rapid progressive central vision loss with ↓ acuity and colour vision	Late visual loss	Unilateral acute field defect with ↓ colour vision	Unilateral variable vision loss
Symptoms	Pain (esp with eye movement)	Headache, N/V, local neurological deficits	If GCA: headache, scalp tenderness, jaw claudication	Cardiovascular risk factors
Pupil	RAPD	No RAPD	RAPD	No RAPD
Fundus	Disc swelling if anterior	Disc swelling, retinal hemorrhage, no venous pulsations	Pale segmental disc edema, retinal dot, flame hemorrhages	Swollen disc, venous engorgement, retinal hemorrhage
Etiologies	MS, viral	Increased ICP	Giant cell arteritis	Associated with vasculopathy
Treatment	IV (not oral) methylprednisolone	Treat cause	Consider ASA if non-arteritic; steroids if arteritic	optimize risk factors, reduce IOP, ± laser

Abbreviations: AION – anterior ischemic optic neuropathy; CRVO – central retinal vein occlusion; RAPD – relative afferent pupillary defect

Optic Disc Atrophy

- **etiologies:** glaucoma, AION, compressive tumour, optic neuritis, Leber's hereditary optic neuropathy, congenital
- **presentation:** disc pallor, low visual acuity, peripheral vision defect, decreased colour vision
- **treatment:** none (irreversible), aim to prevent

Abnormalities of Visual Field

Definitions

- **monocular**
 - scotoma: an area of absent or diminished vision within an otherwise intact visual field
- **binocular**
 - hemianopsia: loss of half of the visual field
 - homonymous: loss of either the right or left half of the visual field in both eyes
 - bitemporal: loss of both temporal visual fields (lesion of chiasm)
 - quadrantanopsia: loss of one quarter of the visual field

BITEMPORAL HEMIANOPSIA

- chiasmal lesion
 - in children: craniopharyngioma
 - in middle aged: pituitary mass
 - in elderly: meningioma

HOMONYMOUS HEMIANOPSIA

- retrochiasmal lesion
- the more congruent, the more posterior the lesion
- check all hemiplegic patients for ipsilateral homonymous hemianopsia (e.g. left hemisphere → right visual field defect)

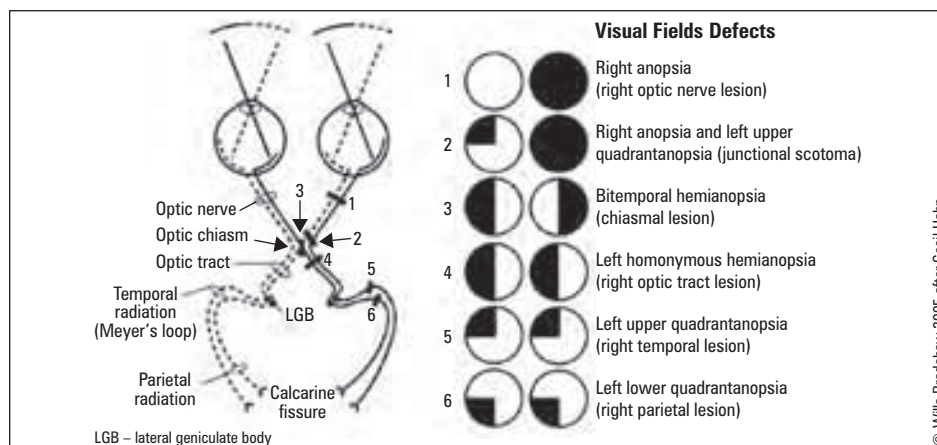


Figure 16. Characteristic Visual Field Defects with Lesions Along the Visual Pathway

Abnormalities of Eye Movements

Disorders of Lateral Gaze

Etiology

- brainstem infarcts
- multiple sclerosis
- tumours

Pathophysiology

- voluntary eye movements are triggered in the frontal eye fields, located anterior to the precentral gyrus, bilaterally in the frontal lobes
- each frontal eye field controls voluntary saccades to the contralateral side via connections to the contralateral paramedian pontine reticular formation (PPRF)
- a unilateral lesion in one frontal eye field: prevents voluntary saccades to the opposite side, eyes deviate toward the side of the lesion
 - can be overcome with doll's eye maneuver
- a unilateral lesion in the PPRF in the pons: prevents voluntary saccades to the ipsilateral side, eyes deviate away from the lesion
 - cannot be overcome with doll's eye maneuver
- seizure involving a frontal eye field: cause eye deviation towards the opposite side



A lesion in a cerebral hemisphere causes eyes to "look away" from the hemiplegia, and to look towards the lesion.

A lesion in the brainstem causes the eyes to "look toward" the side of the hemiplegia, and to look away from the lesion.

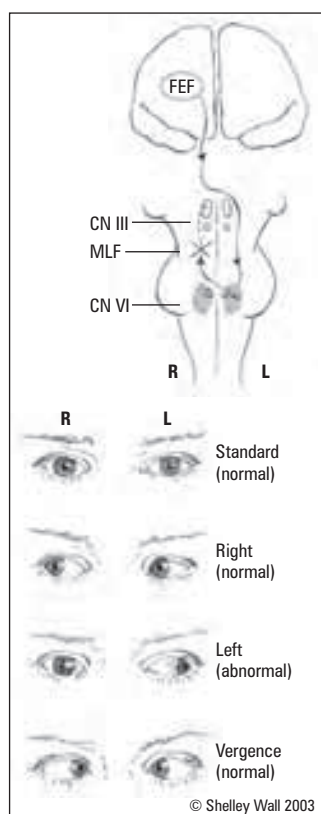


Figure 17. Internuclear Ophthalmoplegia



Diplopia worse at end of the day suggests myasthenia gravis (e.g. fatiguable).



If only diplopia on extremes of gaze, cover each eye in isolation during extremes of gaze.

The covered eye that makes the outermost image disappear is the one with pathology.

Internuclear Ophthalmoplegia (INO)

Etiology

- MS (most common; see *Multiple Sclerosis*, N49)
- brain stem infarction
- neoplasm
- AV malformations
- Wernicke's encephalopathy

Pathophysiology

- results from a lesion in medial longitudinal fasciculus (MLF) which disrupts coordination between CN VI nucleus in pons and the contralateral CNIII nucleus in midbrain → disrupts conjugate horizontal gaze

Clinical Features

- on gaze away from the side of the lesion:
 - 1) adduction of ipsilateral eye is impaired; 2) full excursion of contralateral eye in abduction but with monocular abduction nystagmus
 - cannot be overcome by caloric testing
 - accommodation reflex intact
- may be bilateral
- upbeating nystagmus on upward gaze often present

Diplopia

Monocular

- mostly due to relatively benign optical problems (refractive error, cataract, functional)

Binocular

- cranial nerve palsy (see *Cranial Nerves*, N17)
 - CN III (oculomotor)
 - ♦ DM, aneurysm, tumour, trauma
 - ♦ isolated CN III palsy with pupil sparing usually due to DM and most will resolve spontaneously in several months
 - ♦ isolated CN III palsy with pupil involved usually indicates compressive lesion (especially posterior communicating artery aneurysm)
 - CN IV (trochlear)
 - ♦ DM, trauma
 - CN VI (abducens)
 - ♦ DM, tumour, trauma, raised ICP (false localizing sign)
 - muscle
 - ♦ Graves' ophthalmopathy
- neuromuscular junction
 - myasthenia gravis (MG) (see *Myasthenia Gravis*, N32)
- other
 - orbital trauma, tumour
 - Wernicke's encephalopathy
 - Miller-Fischer variant of GBS
 - leptomeningial disease

Nystagmus

- definition: rapid, involuntary, small amplitude movements of the eyes that are rhythmic in nature
- direction of nystagmus is defined by the rapid component of the eye movement
- can be categorized by movement type (pendular, jerking, rotatory, coarse) or as normal vs. pathological

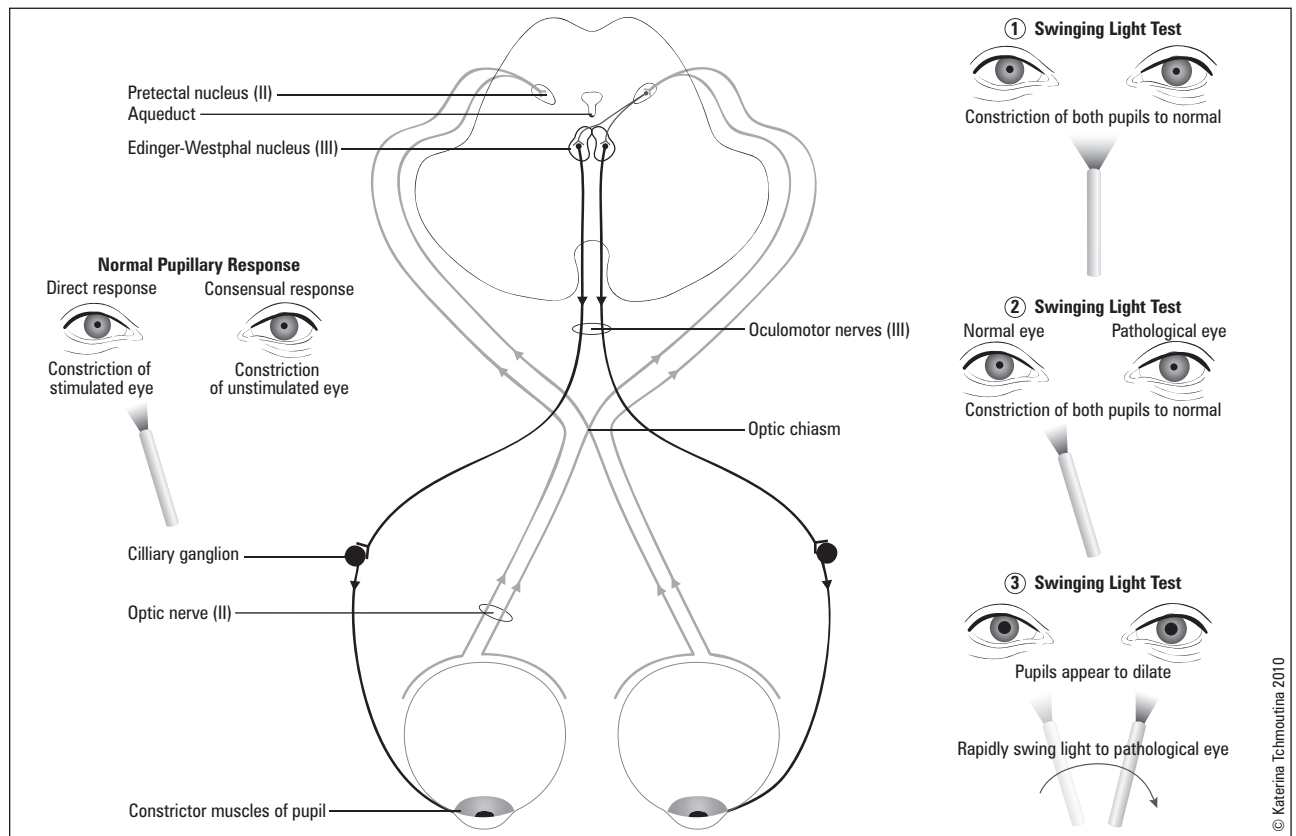
Abnormalities of Pupils

Relative Afferent Pupillary Defect (RAPD) (Marcus-Gunn Pupil)

- see also Ophthalmology, OP33

Definition

- a failure of direct pupillary responses to light, caused by a defect in the visual afferent pathway anterior to the optic chiasm
- clinical testing
 - swinging light test
 - ♦ swing light from one eye to the other; both pupils should constrict initially
 - ♦ when normal side is illuminated, both pupils constrict
 - ♦ when damaged side is illuminated, both pupils paradoxically dilate because the damaged eye perceives less light relative to normal eye
 - pupil reacts poorly to light, and better to accommodation
- differential diagnosis
 - optic neuritis is the most common cause of RAPD
 - other causes: optic nerve compression, large retinal detachment, central retinal artery/vein occlusion, advanced glaucoma



Horner's Syndrome

Definition

- a sympathetic defect
- clinical features: partial ptosis (drooping eyelid), miosis (constricted pupil), anhydrosis (lack of sweating), and apparent enophthalmos
- lesions occur anywhere along the sympathetic pathway on the affected side
 - 1st-order neuron (central): hypothalamus, medulla (brainstem stroke), spinal tumour, MS, intracranial tumours, syringomyelia
 - 2nd-order neuron (preganglionic): apical lung cancer (Pancoast's tumour), paravertebral mass, carotid artery dissection
 - 3rd-order neuron (postganglionic): cluster headache, cavernous sinus mass, trauma (including surgical)
- clinical confirmation with cocaine test: cocaine does not dilate a miotic Horner's pupil. Cocaine blocks the reuptake of noradrenaline, which dilates a normal pupil
- central vs. pre-ganglionic vs. post-ganglionic
 - paredrine (hydroxyamphetamine, stimulates noradrenaline release) will not dilate in a case of post-ganglionic lesion, but will dilate if there is a pre-ganglionic or central lesion
 - no test to differentiate central from pre-ganglionic lesion



Horner's Syndrome

- Ptosis
- Miosis
- Anhydrosis

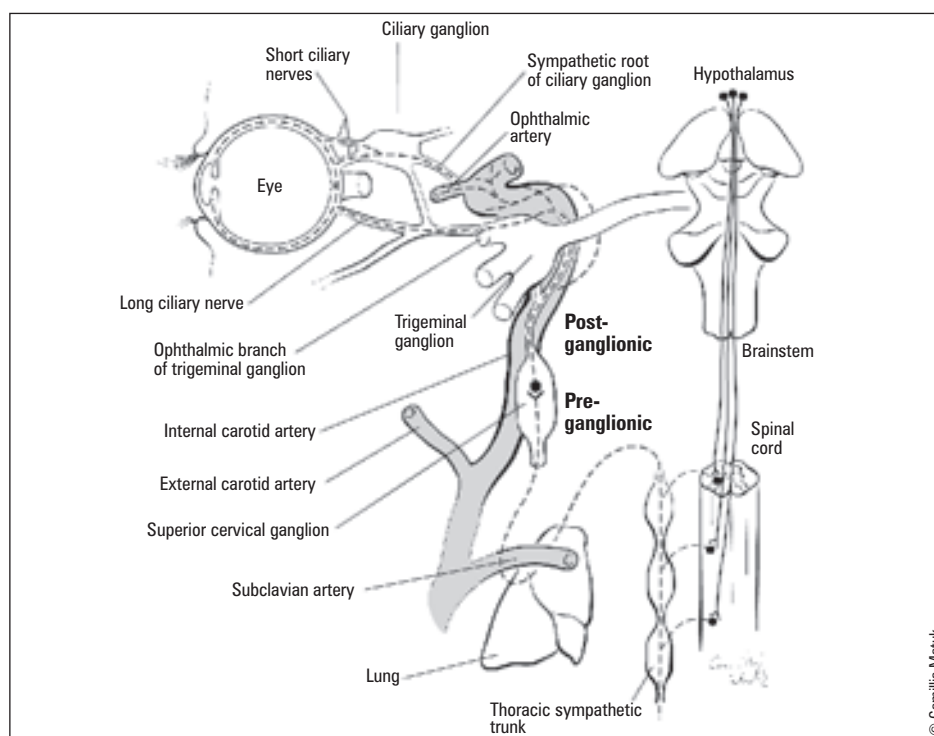


Figure 19. Sympathetic Pathway of Pupillary Dilation

Anisocoria

- **definition:** unequal size of the pupils
- see Ophthalmology, OP31

Movement Disorders



Overview of Movement Disorders

Table 16. Movement Disorder Definitions

Akathisia	Subjective restlessness relieved by stereotypic movements (e.g. squirming)
Asterixis	Loss of muscle contraction (negative myoclonus)
Athetosis	Slow writhing movements, especially distally
Bradykinesia	Slow and/or small amplitude movements
Chorea	Rapid jerky movement that looks semi-purposeful
Dyskinesia	Excessive movements associated with neuroleptics
Dystonia	Co-contraction of agonist and antagonists causing sustained twisting movements
Freezing	Episodes of halted motor action, especially during walking
Hemiballism	Unilateral violent flinging movement
Myoclonus	Brief muscle group contraction that is either focal, segmental, or generalized
Myokimia	Muscle quivering
Tachykinesia	Acceleration of movements
Tics	Stereotyped repetitive actions due to inner urge; can be suppressed
Tremor	Rhythmic alternating movements



Describing Movement

Hyperkinesia: excess of movement (i.e. most movements seen in movement disorders)

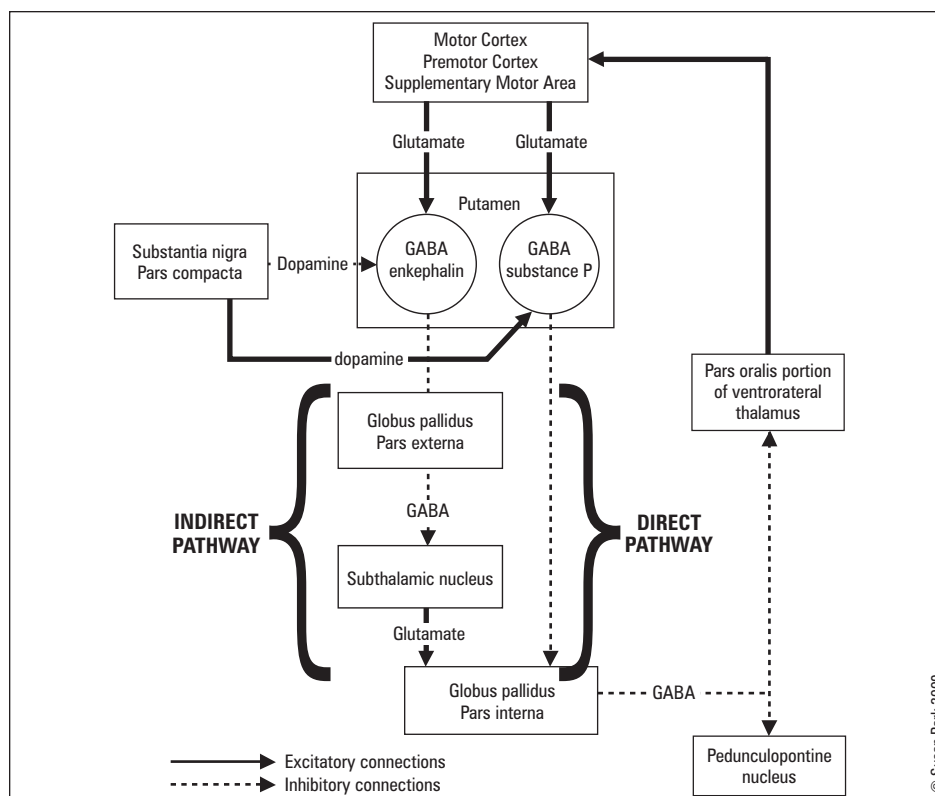
Hypokinesia: reduction in movement (i.e. bradykinesia and freezing)



Some myoclonus is stimulus sensitive and can be induced by noise, movement, light, visual threat, or pinprick.

Function of the Basal Ganglia

- the striatum (caudate and putamen) is the input of the basal ganglia. It receives input from the cortex and thalamus to inhibit the globus pallidus pars interna (GPi) and substantia nigra reticularis (SNr), promoting movement
- the GPi and SNr are the output of the basal ganglia. They project fibres to the cortical motor areas via the ventral thalamus (thalamocortical) to prevent excess movement using tonic inhibition (in particular the GPi)
- the cerebral cortex initiates movement via excitatory (glutamatergic) projections to the striatum, which then activate two pathways: direct and indirect
- indirect: cortex → striatum → GPe → STN → GPi/SNr → thalamus → motor cortex
 - activation of this pathway causes inhibition of the thalamus and ultimately prevents movement
- direct: cortex → striatum → GPi/SNr → thalamus → motor cortex
 - activation of this pathway removes the inhibitory effect of the GPi on the thalamus, thereby allowing movement



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Figure 20. Neural Connections of the Basal Ganglia

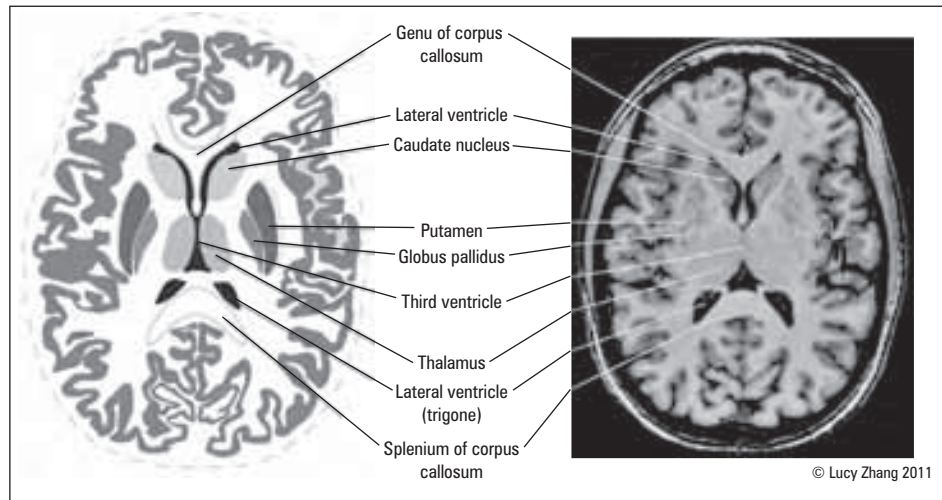


Figure 21. Horizontal Section of Basal Ganglia



In a young patient (<45) must do TSH (thyroid disease), ceruloplasmin (Wilson's disease), and CT/MRI (cerebellar disease) as indicated by type of tremor.



Alcohol dampens essential tremor. Alcohol potentiates intention tremor.



>90% of essential tremor does not need treatment.



Most common cause of chorea is drug therapy for Parkinson's disease.

Approach to Movements Disorders

1. Describe the movements. Classify each as hyperkinesias or hypokinesias
2. Name the movements (see Table 16)
3. Consider the differential diagnoses for the movements named

Differential Diagnoses

1. Tremor:

- a. Postural: physiologic, anxiety, sedative/alcohol withdrawal, drug toxicity, heavy metal poisoning, carbon monoxide poisoning, thyrotoxicosis, benign essential tremor, cerebellar, Wilson's disease
 - ♦ benign essential tremor is a common autosomal dominant trait that presents as a bilateral postural tremor of the vertical axis, especially in the upper extremities
- b. Intention: brainstem lesion, cerebellar lesion, alcohol, anticonvulsants, sedatives, Wilson's disease
- c. Resting: Parkinsonism, Wilson's disease, mercury poisoning

Table 17. Approach to Tremors

	Resting	Postural	Intention
Body Part	Distal UE	UE/head/voice	Anywhere
Characteristics	3-7Hz pill rolling	6-12Hz fine tremor	<5Hz coarse tremor
Worse with	Rest while concentrating	Sustained posture (outstretched arms)	Finger to nose
Associated Sx	"TRAP"	± Autosomal dominant FHx	Cerebellar findings
DDx	IPD, Parkinsonism, Wilson's disease	Physiologic, benign essential, drugs, hyperthyroid, hyperglycemic	Cerebellar disorders, Wilson's disease, alcohol, MS
Treatment	Sinemet, anticholinergics, surgery, DBS	Propranolol, anticonvulsants, primidone	Treat underlying cause

2. **Chorea:** Huntington's disease, neuroacanthocytosis, SLE, APLA syndrome, Wilson's disease, cerebrovascular disease, tardive dyskinesia, senile chorea, Sydenham's chorea, pregnancy chorea

3. Dystonia

- a. Primary dystonia: familial, sporadic (torticollis, blepharospasm, writer's cramp)
- b. Dystonia-plus syndromes: dopa-responsive dystonia, myoclonus-dystonia
- c. Secondary dystonia: thalamotomy, stroke, CNS tumour, demyelination, PNS injury, drugs/toxins (L-dopa, neuroleptics, anticonvulsants, Mn, CO, cyanide, methanol)
- d. Heterodegenerative dystonias: Parkinsonian disorders, Wilson's disease, Huntington's disease

4. Tics

- a. Primary tic disorders: transient tic disorder, chronic tic disorder, Gilles de la Tourette, adult onset or senile
- b. Secondary tic disorders: encephalitis, CJD, Sydenham's chorea, head trauma, drugs, mental retardation syndromes
- c. Association with OCD and ADHD

Parkinson's Disease (PD)

Etiology

- **sporadic:** combination of oxidative stress to dopaminergic neurons, environmental toxins (e.g. pesticides), accelerated aging, genetics
- **familial (10%):** autosomal dominant α -synuclein mutations, autosomal recessive Parkin gene or DJ-1 gene mutation (juvenile onset)
- **MPTP** (neurotoxin)

Pathophysiology

- loss of dopaminergic neurons in pars compacta of substantia nigra, thus reduced dopamine in striatum leading to disinhibition of the indirect pathway and decreased activation of the direct pathway causing increased inhibition of cortical motor areas
- α -synucleinopathy: α -synuclein accumulates in Lewy bodies and causes neuritis in substantia nigra

Signs and Symptoms

- positive motor
 - rest tremor: asymmetric 4-5Hz "pill-rolling" tremor, especially hands
 - rigidity: lead-pipe hypertonus; cogwheeling due to superimposed tremor
- negative motor
 - bradykinesia: slow small amplitude movements, difficulty initiating movement
- related findings: masked facies, hypophonia, aprosody (monotonous speech), dysarthria, micrographia, shuffling gait with decreased arm swing
- freezing: occurs with walking triggered by initiating stride or barriers/destinations, lasts seconds
- postural instability: late finding of falls, shuffling gait with acceleration and flexed body
- cognition: bradyphrenia (slow to think/respond), late finding of dementia
- behavioural: personality change, decreased spontaneous speech, depression, sleep disturbances, anxiety
- autonomic: later findings of constipation, urinary retention, sexual dysfunction

Treatment

- pharmacologic
 - mainstay of treatment: Sinemet® (levodopa/carbidopa). Levodopa is a dopamine precursor, carbidopa decreases peripheral conversion to dopamine
 - treatment of early PD: DA agonists, amantadine, MAOI
 - adjuncts: DA agonists, MAOI, anticholinergics (especially if prominent tremors), COMT inhibitors
- surgical: thalamotomy, pallidotomy, deep brain stimulation (thalamic, pallidal, subthalamic), embryonic dopaminergic stem cell transplantation
- levodopa related fluctuation: delayed onset of response (affected by mealtime), end-of-dose deterioration (i.e. "wearing-off"), random oscillations of on-off symptoms
- major complication of levodopa therapy is dyskinesias
- psychiatric (see [Psychiatry](#))



Key Parkinsonian Features

TRAP

Tremor
Rigidity
Akinesia/bradykinesia
Postural instability



Consider an Alternative Diagnosis if Atypical Parkinsonism

- Poor response to L-dopa
- Abrupt onset of symptoms
- Rapid progression
- Early falls
- Early autonomic dysfunction
- Symmetric symptoms at onset
- Early age of onset (<50)
- Early cognitive impairment
- FHx of psychiatric/dementing disorders
- Recent diagnosis of psychiatric disease
- History of encephalitis
- Unusual toxin exposure
- Extensive travel history

Other Parkinsonian Disorders

- **parkinsonism:** akinesia (bradykinesia and low amplitude) often accompanied by rigidity. Tremor is an optional feature, as is postural instability
- **Lewy Body disease** (see *Behavioural Neurology*, N13)
- **progressive supranuclear palsy:** tauopathy with limited vertical gaze (classically downgaze), early falls, axial rigidity and akinesia, dysarthria and dysphagia
- **corticobasal degeneration:** tauopathy with varied presentations but classically presents with unilateral parkinsonism, dystonia/myoclonus, apraxia \pm "alien limbs" phenomenon
- **multiple system atrophy:** synucleinopathy presenting as either cerebellar predominant (previously olivo-ponto cerebellar atrophy or OPCA) or parkinsonism predominant (previously striato-nigral degeneration). Both are associated with early autonomic dysfunction (previously Shy-Drager syndrome)
- **vascular parkinsonism:** multi-infarct presentation with lower body parkinsonism

Huntington's Disease

Etiology and Pathogenesis

- genetics: autosomal dominant CAG repeat disorder with anticipation of Huntington gene on chromosome 4 leading to accumulation of defective protein in neurons
- pathology: global cerebral atrophy, especially affects the striatum, leading to increased activity of the direct pathway and decreased activity of the indirect pathway

Epidemiology

- North American prevalence 4-8/100,000
- mean age of onset 35-44 years; but varies with degree of anticipation from 5-70

Signs and Symptoms

- typical progression: insidious onset with clumsiness, fidgetiness, irritability progressing over 15 years to frank dementia, psychosis and chorea
- chorea: begins as movement of eyebrows and forehead, shrugging of shoulders, and parakinesia (pseudopurposeful movement to mask involuntary limb jerking)
 - progresses to dance-like or ballism, and in late stage is replaced by dystonia and rigidity
- dementia: progressive memory impairment and loss of intellectual capacity
- mood changes: irritability, depression, anhedonia, impulsive, bouts of violence
- psychosis
- juvenile onset (Westphal variant): begins in adolescence with bradykinesia and rigidity with a severe progressive course spanning 5 to 10 years

Investigations

- MRI: enlarged ventricles, atrophy of cerebral cortex and caudate nucleus
- genetic testing

Treatment

- no disease altering treatment
- psychiatric symptoms: antidepressants and antipsychotics
- chorea: neuroleptics and benzodiazepines
- dystonia: botulinum toxin

Dystonia

Epidemiology

- most common movement disorder encountered in movement disorder clinics after parkinsonism

Features

- worse with fatigue, stress, emotions; relieved by sleep or specific tactile/proprioceptive stimuli ('geste antagoniste', e.g. place hand on face for cervical dystonia)
- more likely to be progressive and generalize if younger onset or if leg dystonia

Treatment

- local medical: botulinum toxin
- systemic medical: anticholinergics, muscle relaxants (Baclofen), benzodiazepines, antidopaminergics (reserpine, neuroleptics); dopamine for dopa-responsive dystonia
- surgical: surgical denervation of affected muscle, stereotaxic thalamotomy (unilateral dystonia), posteroventral pallidotomy



Botulinum toxin (BOTOX) acts by preventing ACh release at the neuromuscular junction.

Tic Disorders

Clinical Classification

- motor tics
 - simple: blinking, head jerking
 - dystonic: bruxism, grinding teeth, abdominal tension, sustained mouth opening
 - complex: copropraxia (obscene gestures), echopraxia (imitate gestures), throwing, touching
- vocal tics
 - simple: blowing, coughing, grunting, throat clearing
 - complex: coprolalia (shout obscenities), echolalia (repeat others' phrases), palilalia (repeat own phrases)

Treatment

- dopamine blocker

Tourette's Syndrome (aka Gilles de la Tourette's Syndrome)



Definition according to DSM IV

1. Presence of motor and vocal tic at some point during illness, not necessarily concurrently
2. Multiple tics a day nearly everyday or intermittently throughout 1 year with no tic-free periods greater than 3 months
3. Onset prior to 18 years of age
4. Not due to effect of a substance or general medical condition

Epidemiology

- prevalence among adolescents 3-5/100,000; M>F

Signs and Symptoms

- tics: wide variety that wax and wane in type and severity
 - can be voluntarily suppressed for some time but are preceded by unpleasant sensation that is relieved once tic is carried out
- psychiatric: compulsive behaviours (associated with OCD and ADHD), hyperactive behaviour, 'rages', sleep-wake disturbances, learning disabilities

Treatment

- clonidine, clonazepam

Prognosis

- Begins at 5 years progressively increasing until 10 years; often improves in adolescence and 50% are tic-free by 18 years

Motor Neuron Disease

Amyotrophic Lateral Sclerosis (ALS) (aka Lou Gehrig's Disease)

Definition

- progressive degeneration of motor neurons causing UMN and LMN symptoms

Etiology

- genetic (5-10% familial, especially SOD1 mutation), viral, autoimmune paraneoplastic, glutamate toxicity, idiopathic

Pathology

- degeneration and loss of motor neurons with astrocytic gliosis
- bunina bodies (eosinophilic hyaline intracytoplasmic inclusions) in 70%
- disorder of anterior horn cells of spinal cord, cranial nerve nuclei, and corticospinal tract

Epidemiology

- 5/100,000 with onset between 40-60 (earlier if familial)

Signs and Symptoms

- limb motor symptoms: segmental and asymmetrical UMN and LMN symptoms of limbs
- bulbar findings: dysarthria, dysphagia, tongue atrophy and fasciculations
- pseudobulbar affect or emotional lability
- sparing of ocular muscles and of sphincters

Investigations

- EMG: denervation (3 limbs + paraspinal), reinnervation, fasciculations
- muscle biopsy: small angulated fibres (i.e. denervation), fibre-type grouping
- rule out cord disease/compression with CT or MRI

Management

- disease specific: riluzole
- muscle stiffness/spasticity: baclofen, tizanidine
- sialorrhea: TCA (e.g. amitriptyline), anticholinergics (e.g. scopolamine patch)
- pseudobulbar affect: dextromethorphan/quinidine, TCA, SSRI
- non-pharmacologic: ventilatory support (e.g. BiPAP), early nutritional support, rehabilitation (PT, OT, SLP), psychosocial support

Prognosis

- median survival 3 years (longer if ventilatory support), death due to respiratory failure



Red Flags inconsistent with ALS

Sensory sx, predominant pain, bowel or bladder incontinence, cognitive impairment, ocular muscle weakness.



Denervation on EMG

Fibrillations, positive sharp waves, complex repetitive discharges; reinnervation – increased amplitude and duration of motor units.

Other Motor Neuron Diseases

- **progressive muscular atrophy (progressive bulbar palsy)**: only LMN symptoms with asymmetric weakness, later onset than ALS, 5-10% of patients in ALS centres
- **primary lateral sclerosis (progressive pseudobulbar palsy)**: UMN symptoms, later onset, not fatal with variable disability; 5-10% of patients in ALS centres
- **spinal muscular atrophy**: pediatric disease with symmetric LMN symptoms
- **post-polio syndrome**: residual asymmetric muscle weakness, atrophy
- **multifocal motor neuropathy**: conduction block on NCS, asymmetric LMN symptoms, \pm anti-GM1 Ab, treatable with IVIg



Peripheral Neuropathies



DDx of Mononeuropathy Multiplex

Vasculitis (e.g. PAN), DM, leprosy, sarcoidosis, HIV, lymphoma, Lyme disease, pressure palsy predisposition (hereditary), multifocal motor neuropathy (pure motor), chronic inflammatory demyelinating polyneuropathy (CIPD).



Diabetic Neuropathies

1. Axonal (most common): pain > motor
2. Autonomic: anhidrosis, orthostatic hypotension, impotence, gastroparesis, bowel and bladder dysfunction
3. Mononeuropathy multiplex: nerve infarct or compression
4. Cranial neuropathy: CNIII (pupil sparing) > IV > VI



DDx of Demyelinating Neuropathy

GBS, CIDP, paraproteinemia, diphtheria, amiodarone, charcot-marie-tooth, storage diseases, pressure palsy predisposition, paraneoplastic.



Axonal neuropathies have decreased amplitude on NCS; demyelinating neuropathies have decreased velocity on NCS.



Ototoxic drugs (e.g. aminoglycosides) should not be given to diabetics. Sensory neuropathy of feet prevent them from adequately compensating for loss of vestibular function.

- **monoradiculopathy**: dermatomal deficit due to single nerve root lesion
 - due to disc herniation or root compression causing radicular pain
- **polyradiculopathy**: multiple dermatome deficits due to multiple nerve root lesions
 - most common cauda equina syndrome (i.e. lumbosacral roots)
- **plexopathy**: deficit matching distribution of a nerve plexus
 - brachial plexopathy
 - ♦ upper (C5-C7): LMN sx of shoulder and upper arm muscles (Erb's palsy)
 - ♦ lower (C8-T1): LMN sx and sensory sx of forearm and hand (Klumpke's palsy)
 - ♦ DDx: trauma, idiopathic neuritis, tumour infiltration, radiation, thoracic outlet syndrome (i.e. cervical rib)
 - lumbosacral plexopathy (rare, especially unilateral)
 - ♦ DDx: idiopathic neuritis, infarction (i.e. diabetes), compression
- **mononeuropathy**: single nerve deficit
 - carpal tunnel syndrome (most common): compression of median nerve at wrist
 - ♦ symptoms: wrist pain, paresthesia first 3 digits, \pm radiation to elbow, worse at night
 - ♦ signs: Tinel's sign, thenar muscle wasting, sensory deficit
 - ♦ EMG and NCS: slowing at wrist (both motor and sensory)
 - Bell's Palsy (most common cranial neuropathy): see Otolaryngology, OT23
 - other less common mononeuropathies due to entrapment/compression: ulnar (compression at elbow), median (at pronator teres), Saturday night palsy (radial nerve entrapment at spiral groove of humerus), obturator (from childbirth), peroneal (due to crossing legs or surgical positioning), posterior tibial (tarsal canal)
- **mononeuropathy multiplex**: deficit affecting multiple discrete nerves (asymmetric)
 - most commonly due to diabetes
- **polyneuropathy**: symmetrical distal stocking-glove pattern
 - presentation: symmetrical distal sensorimotor deficit affecting longest fibres first (i.e. stocking-glove distribution), hypotonia; progression of dysesthesia early, weakness later
 - most polyneuropathies are due to medical conditions like diabetes, renal disease, substances, toxins, or are hereditary
 - other important etiologies: SLE, HIV, leprosy, alcohol, B₁₂ deficiency, uremia
 - chronic inflammatory demyelinating polyneuropathy (CIDP)
 - ♦ chronic relapsing sensorimotor polyneuropathy with increase protein in CSF and demyelination (shown on EMG/NCS)
 - ♦ course is fluctuating compared to acute onset of GBS
 - ♦ treatment: firstline is prednisone: alternatives are plasmapheresis, IVIg, and asathioprine
 - critical illness polyneuropathy
 - ♦ associated with sepsis and multisystem organ failure; severe sensorimotor axonal neuropathy

Table 18. Differential Diagnosis of Symmetric Polyneuropathy*

	Etiology ⁺	Mechanism	Course	Modalities	Investigations
Vascular	PAN	Ischemic	Chronic	S/M	see <u>Rheumatology</u> , RH17
	SLE	Ischemic	Chronic	S/M	see <u>Rheumatology</u> , RH9
	RA	Ischemic	Chronic	S/M	see <u>Rheumatology</u> , RH6
Infectious	HIV	Axonal/demyelination	Chronic	S/A	HIV serology
	Leprosy	Infiltrative	Chronic	S/A	Leprosy serology Nerve biopsy
	Lyme	Axonal/demyelination	Chronic	M	Lyme serology
Immune	GBS	Demyelination	Acute	M	LP (\uparrow protein; no \uparrow cells)
	CIDP	Demyelination	Chronic	S/M	LP (\uparrow protein)

Table 18. Differential Diagnosis of Symmetric Polyneuropathy* (continued)

	Etiology⁺	Mechanism	Course	Modalities	Investigations
Hereditary	HMSN	Axonal/demyelination	Chronic	S/M	Genetic testing
Neoplastic	Paraneoplastic	Axonal/demyelination	Chronic	S/M	Anti-Hu
	Myeloma	Axonal/demyelination	Chronic	S/M	SPEP Skeletal bone survey
	Lymphoma	Axonal	Chronic	M	SPEP Bone marrow biopsy
	Monoclonal gammopathy	Demyelination	Chronic	S/M	SPEP Bone marrow biopsy
Toxin	<i>EtOH</i>	Axonal	Sub-acute	S/M	GGT
	Heavy metals	Axonal	Sub-acute	S/M	Urine heavy metals
	Medications	Axonal	Sub-acute	S/M	Drug levels
Metabolic	<i>Diabetes</i>	Ischemic/axonal	Chronic	S/A	Fasting glucose, HbA1C, 2hr OGTT
	Hypothyroidism	Axonal	Chronic	S/M	TSH, T ₃ , T ₄
	Renal failure	Axonal	Chronic	S/A	Lytes, Cr, BUN
Nutritional	<i>B₁₂ deficiency</i>	Axonal	Sub-acute	S/M	Vitamin B ₁₂
Other	Porphyria	Axonal	Sub-acute	M	Urine parphyrins
	Amyloid	Axonal	Sub-acute	S	Nerve biopsy

*Abbreviations: GBS – Guillain-Barré Syndrome; PAN – polyarteritis nodosa; SLE – systemic lupus erythematosus; RA – rheumatoid arthritis; CIDP – chronic inflammatory demyelinating polyradiculoneuropathy; HMSN – hereditary motor sensory neuropathy; SPEP – serum protein electrophoresis; S – sensory; M – motor; A – autonomic

+Most common/important etiologies in italics type

Guillain-Barre Syndrome (GBS)

- **definition:** acute rapidly evolving polyneuropathy
- **risk factors and etiology**
 - pathophysiology suspected to be focal inflammation
 - viral/bacterial infections and vaccinations, have been shown to predispose to GBS
- **signs and symptoms**
 - sensory: distal and symmetric paresthesias, loss of proprioception and vibration sense, pain
 - motor: weakness starting distally in legs, areflexia
 - autonomic: blood pressure dysregulation, arrhythmias, bladder dysfunction
- **investigations**
 - CSF: albuminocytological dissociation (high protein, normal WBC)
 - EMG/NCS: conduction block, differential or focal (motor>sensory) slowing, decreased F-wave
- **subtypes**
 1. Acute inflammatory demyelinating polyneuropathy (AIDP)
 2. Acute motor-sensory axonal neuropathy (AMSAN)
 3. Acute motor axonal neuropathy (AMAN)
- **treatment**
 - disease specific: IVIg or plasmapheresis
 - nonpharmacologic: admit and monitor vital signs and vital capacity due to risk of respiratory failure, manage dysautonomia, manage pain
- **prognosis**
 - nadir of symptoms at 2-3 weeks, with resolution at 4-6 weeks
 - 5% mortality (higher if ICU), 7-15% permanent substantial deficits



GBS is a neurological emergency due to risk of imminent respiratory failure.



Miller-Fischer Variant of GBS – Triad
 1. Ophthalmoplegia
 2. Ataxia
 3. Areflexia



IVIg and plasmapheresis lead to more rapid improvement, less intensive care and less ventilation, but do not change mortality or relapse rate.

Diagnostic Approach to Peripheral Neuropathies

1. **Differentiate:** motor vs. sensory vs. autonomic
2. **Pattern of Deficit:** symmetry, focal vs. diffuse, upper vs. lower limb, cranial nerve involment
3. **Tempo:** acute to chronic, relapsing remitting vs. constant
4. **Good History:** PMH, detailed family tree, exposures (e.g. insects, toxins, sex, travel), systemic symptoms
5. **Detailed Peripheral Neuro Exam:** LMN findings, differentiate between root and peripheral nerves, check cranial nerves, check respiratory status

Neuro-oncology

Paraneoplastic Syndromes

Definition

- uncommon complication of cancer; often is the presenting complaint

Pathophysiology

- likely an autoimmune attack on the nervous system by tumour antigens

Associated Neoplasms

- small cell lung cancer: cerebellar degeneration, encephalitis, opsoclonus-myoclonus, retinopathy, neuropathy, Lambert-Eaton syndrome
- breast: cerebellar degeneration, encephalomyelitis, opsoclonus-myoclonus
- thymoma: myasthenia gravis
- other syndromes: necrotizing myelopathy, motor neuron syndrome, neuropathies, mononeuritis multiplex, polymyositis and dermatomyositis, encephalitis

Investigations

- antibodies commonly ordered include anti-Hu, anti-Ri and anti-Yo

Treatment

- unsatisfactory and often palliative. Options to consider are steroids, IVIg, plasmapheresis and treatment of malignancy

Tumours of the Nervous System

- see [Neurosurgery](#), NS9

Neuromuscular Junction Diseases

Clinical Approach to Disorders of the Neuromuscular Junction

Table 19. Common Disorders of the Neuromuscular Junction

	Myasthenia Gravis	Lambert-Eaton	Botulism
Ocular/bulbar paresis	+	–	++ (early)
Limb weakness	+	+	+
Fatiguability	+	+	+
Post-exercise enhancement	–	+	+
Reflexes	N	↓	↓
ANS anticholinergic Sx	–	+	++
Sensory Sx	–	–	–
Associated conditions	Thymoma	Small cell carcinoma	GI SSx
Repetitive EMG stimulation	↓	↑ (rapid stimulation) ↓ (slow stimulation)	↑ (rapid stimulation) ↓ (slow stimulation)



Diseases of the neuromuscular junction typically feature prominent fatiguability.

Myasthenia Gravis (MG)

Etiology and Pathophysiology

- damage and blockade of post-synaptic acetylcholine receptors by specific antibodies
- 15% of patients with myasthenia gravis have associated thymic neoplasia, 85% have thymic hyperplasia
- autoimmune disorder

Epidemiology

- bimodal age of onset – 20's (mostly women) and 60's (mostly men)

Signs and Symptoms

- see also Table 19
- fatigability and weakness of skeletal muscles without reflex, sensory, or coordination abnormalities
- typically ocular (diplopia/ptosis) → bulbar (dysarthria/dysphagia) → neck flexors/extensors → proximal limbs
- respiratory muscle weakness may lead to respiratory failure

Investigations

- edrophonium (Tensilon®) test – can result in respiratory difficulty so have crash cart nearby
 - assess for improvement over 2 minutes following edrophonium injection
- EMG
 - repetitive stimulation → decremental response
 - single fibre electromyography shows increased jitter (80-100% sensitivity)
- anti-acetylcholine receptor antibody assay (70-80% sensitivity)
- MUSK antibody may be used if seronegative for AChR antibody
- CT/MRI to screen for thymoma/thymic hyperplasia

Treatment

- thymectomy
 - 85% of patients show improvement or remission
- symptomatic relief
 - acetylcholinesterase inhibitors (e.g. pyridostigmine)
 - does not affect primary pathologic process → rarely result in control of disease when used alone
- immunosuppression
 - steroids are mainstay of treatment – 70-80% remission rate
 - azathioprine, cyclophosphamide and mycophenolate as adjuncts to steroids or as steroid sparing therapy
- short-term immunomodulation (for crises)
 - IVIg and plasmapheresis

Prognosis

- 30% eventual spontaneous remission



Myasthenia Gravis is a neurological emergency due to the risk of imminent respiratory failure!



Tensilon® is a drug that inhibits acetylcholinesterase. It improves muscle function immediately in myasthenia gravis, but not in cholinergic crisis.



2 Clinical Forms of Myasthenia Gravis

1. Ocular (15%)
2. Generalized (85%)

Lambert-Eaton Myasthenic Syndrome (LEMS)

Etiology and Pathophysiology

- downregulation of presynaptic voltage-gated Calcium channels 2° to specific channel binding antibody causing decreased amounts of ACh released into the synaptic cleft
- 50-66% are ultimately associated with small cell carcinoma of the lung

Signs and Symptoms

- weakness of skeletal muscles without sensory or coordination abnormalities
- reflexes are diminished or absent, but increase after active muscle contraction
- bulbar and ocular muscles affected in 25%
- prominent anticholinergic autonomic symptoms (dry mouth > impotence > constipation > blurred vision)

Investigations

- edrophonium test (see *Myasthenia Gravis*) → no response
- EMG: rapid (> 10Hz) repetitive stimulation → incremental response
- screen for malignancy, especially small cell lung cancer
- post-exercise facilitation – an incremental response to repetitive stimulation due to presynaptic calcium accumulation

Treatment

- tumour removal
- acetylcholine modulation
 - increased acetylcholine release (3-4 diaminopyridine)
 - decreased acetylcholine degradation (pyridostigmine)
- immunomodulation
 - steroids, plasmapheresis, IVIg



Lambert-Eaton myasthenic syndrome can be differentiated from myasthenia gravis, by the phenomenon of post-exercise facilitation.

Myopathies

Clinical Approach to Muscle Diseases

Table 20. Myopathies

	Etiology	Key Clinical Features	Key Investigations
Inflammatory	Polymyositis	Myalgias Pharyngeal involvement	↑ CK Biopsy: endomesial infiltrates; Necrosis
	Dermatomyositis	Myalgias Similar to polymyositis Characteristic rashes Can be paraneoplastic	↑ CK Biopsy: perifascicular atrophy
	Sarcoidosis	See Respirology	ACE level Biopsy: granulomas
	Inclusion body myositis	Weak quads and deep finger flexors	↑ CK Biopsy: inclusion bodies
Endocrine	Thyroid (↑ or ↓) Cushing's syndrome Parathyroid (↑ or ↓)	See Endocrinology	TSH, serum cortisol, calcium panel
Toxic	Medication	Medication or toxin history	Toxicology screen
	Critical illness myopathy	ICU patient Hx steroids and nondepolarizing paralyzing agents Failure to wean from ventilation	Biopsy: selective loss of thick Myosin filaments
Infectious	Parasitic, bacterial, or viral	Myalgias Inflammatory myopathy	↑ myoglobin
Hereditary Dystrophy	Duchenne	Early onset (Duchenne and Becker)	Biopsy: abnormal dystrophin
	Becker	Progressive proximal muscle weakness Calf pseudohypertrophy	Staining
	Myotonic dystrophy	Distal myopathy Myotonia Genetic anticipation	Genetic testing
Hereditary Metabolic	McArdle's	Exercise-related myalgias, cramping, and myoglobulinuria	↑ lactate ↑ serum/urinary myoglobin Post-exercise
Hereditary Periodic Paralysis	Periodic paralysis	Episodic weakness Normal between attacks	↑ or ↓ K
Hereditary Mitochondrial	MERRF	Ptosis, ophthalmoparesis common	Increased lactate
	MELAS	Proximal > distal myopathy	Biopsy: ragged red fibres
	Kearns Sayre	Exercise intolerance Rhabdomyolysis	

*Abbreviations: MERRF – mitochondrial encephalomyopathy with ragged red fibers; MELAS – mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes



Important Information to Know Regarding Myopathies

- Weakness: proximal > distal
- Pain: myalgias, but no impaired sensation
- Myotonia (difficulty with relaxation)



Myopathies are characterized by prominent symmetric proximal weakness and absent sensory changes.



Good Questions to Assess Proximal Weakness

- Legs: climbing stairs, stand from sit
- Arms: reach above head, wash hair



Common Medications that Cause Myopathy

Steroids, statins and antiretrovirals

Polymyositis/Dermatomyositis

- see [Rheumatology](#), RH13

Myotonic Dystrophy

Etiology and Pathophysiology

- unstable trinucleotide repeat in DMK gene (protein kinase) at 19q13.3
- number of repeats correlates with severity of symptoms; autosomal dominant

Epidemiology

- most common adult muscular dystrophy
- prevalence 3-5/100 000

Signs and Symptoms

- appearance: ptosis, bifacial weakness, frontal baldness (including women), triangular face giving a drooping/dull appearance

- physical exam
 - distribution of weakness: distal greater than proximal (in contrast to other myopathic disorders)
 - myotonia: delayed relaxation of muscles after exertion (elicit by tapping on thenar muscles with hammer)
 - cardiac: 90% have conduction defects (1° heart block; atrial arrhythmias)
 - respiratory: hypoventilation 2° to muscle weakness
 - ocular: subcapsular cataracts, retinal degeneration, decreased intraocular pressure
- EMG: subclinical myotonia – long runs with declining frequency and amplitude

Treatment

- no cure
- management of myotonia: phenytoin

Duchenne and Becker Muscular Dystrophy

- see [Pediatrics](#), P46

Cerebellar Disorders

Clinico-Anatomic Correlations

- **vermis:** trunk/gait ataxia
- **cerebellar lobe (i.e. lateral):** tremor, rebound phenomenon, dysarthria, dysdiadochokinesis, nystagmus

Symptoms and Signs of Cerebellar Dysfunction

- nystagmus: observe on extra-ocular movement testing (most common is gaze-evoked nystagmus)
- dysarthria (ataxic dysarthria): abnormal modulation of speech velocity and volume – elicit scanning/telegraphic/slurred speech on spontaneous speech (see *Dysarthria*, N19)
- ataxia: broad-based, uncoordinated, lurching gait
- dysmetria: irregular placement of voluntary limb or ocular movement
- dysdiadochokinesis: unable to perform rapid alternating movements (e.g. pronation – supination task)
- postural instability: look for truncal ataxia on sitting (titubation = rhythmic rocking of trunk and head); look for difficult tandem gait and broad based gait
- intention tremor: elicit on finger-to-nose testing – typically orthogonal to intended movement, and increases as target is approached
- hypotonia: decreased resistance to passive muscular extension- occurs immediately after injury to lateral cerebellum
- pendular patellar reflex: knee reflex causes pendular motion of leg occurs after injury to cerebellar hemispheres
- rebound phenomenon: overcorrection after displacement of a limb (with both arms extended → pushing both will cause one to rebound up if there is lesion on that side)

Wernicke-Korsakoff Syndrome

- deficiency of thiamine due to alcohol abuse
- acute: apathy, confusion, decreased EOM, ataxia (truncal and gait)
 - without treatment progresses to encephalopathy and ultimately death
 - treatment: thiamine 100 mg
- Korsakoff's syndrome: progressive decline of both anterograde and retrograde memory
- note that alcohol can also cause a cerebellar ataxia separate from thiamine deficiency. The ataxia can be due to cerebellar atrophy or alcohol polyneuropathy

Cerebellar Ataxias

Congenital Ataxias

- early onset nonprogressive ataxias associated with various syndromes as well as development abnormalities (e.g. Arnold-Chiari malformation, Dandy-Walker cysts)

Hereditary Ataxias

- **autosomal recessive:** includes Friedreich's ataxia, ataxia telangiectasia, vitamin E deficiency
 - Friedreich's ataxia: prevalence 2/100 000; onset between 8 and 15 years
 - ♦ signs: gait and limb ataxia, weakness, areflexia, extensor plantar reflex, impaired proprioception and vibration
 - ♦ death in 10-20 years from cardiomyopathy or kyphoscoliotic pulmonary restriction
- **autosomal dominant:** spinocerebellar ataxias (SCAs) of which 30 exist, most are CAG repeats

Acquired Ataxias

- neurodegeneration (e.g. multiple system atrophy)
- systemic: alcohol, celiac sprue, hypothyroidism, Wilson's, thiamine deficiency
- toxins: carbon monoxide, heavy metals, lithium, phenytoin, solvents
- vascular: infarct, bleed, basilar migraine
- autoimmune: MS, Miller-Fischer (GBS)
- children: tumours, post-viral

Vertigo

- see Otolaryngology, OT12

**Gait Disturbances****Approach to Gait Disturbances****1. Length of stride**

- if small paces – look at posture
 - if stooped with no armswing – Parkinsonian gait
- look for other signs of extrapyramidal disorders
 - if upright with exaggerated armswing – Marche a petit pas
 - due to diffuse infarction of both cerebral hemispheres (lacunar)

2. If normal stride length, look at width between feet

- if wide-based – ataxia
 - if high stepping and positive Romberg – sensory ataxia
 - loss of joint position sense (+ve Romberg)
- if wide based without high stepping – cerebellar ataxia
 - veers to side of the lesion
- if scissoring of legs or toe walking – spastic gait
 - bilateral circumduction due to spastic paraparesis from cerebral palsy, multiple sclerosis or cord compression

3. If normal width, look for height of step

- if high stepping bilaterally – bilateral foot drop
- if feet barely leave ground or disjointed movement – magnetic/apraxic gait
 - frontal lobe pathology due to normal pressure hydrocephalus or cerebrovascular disease

4. If no high stepping, look for stability of pelvis

- if rotation of pelvis – waddling gait
 - proximal muscle weakness due to congenital deformity or myopathy

5. If no waddling, look at symmetry

- if asymmetric – antalgic gait, deformity or hemiparetic gait
 - antalgic gait is due to pain from an MSK problem
 - hemiparetic gait involves a foot drop and circumduction of spastic leg due to UMN lesion

6. If movement is elaborate and inconsistent, especially when being observed, consider functional gait

- rule out an odd gait due to chorea from Huntington's disease

**CENTRAL MOTOR SYSTEMS****3 components to the control of gait**

- 1. Pyramidal:** main outflow from cortex to spinal cord
- 2. Extrapyramidal:** basal ganglia inhibits excess movements
- 3. Cerebellum:** affects coordination of gait

**Pain Syndromes****Approach to Pain Syndromes****Definitions**

- Nociceptive pain: pain arising from normal activation of peripheral nociceptors
- Neuropathic pain: pain arising from direct injury to neural tissue, bypassing nociceptive pathways
- Spontaneous pain: unprovoked burning, shooting, or lancinating pain
- Paresthesiae: spontaneous or evoked abnormal nonpainful sensations (e.g. tingling)
- Dysesthesiae: spontaneous or evoked pain with inappropriate quality or excessive quantity
- Allodynia: a dysesthetic response to a nonnoxious stimulus
- Hyperalgesia: an exaggerated pain response to a noxious stimulus



- Pinprick causes sharpness mediated by Aδ fibers
- Pain due to tissue damage is mediated by C fibres

Medical Pain Control

- primary analgesics: OTCs, opiates
- adjuvants: antidepressants (TCAs, SSRIs), anticonvulsants (gabapentin, carbamazepine), baclofen, sympatholytics (phenoxybenzamine), α 2-adrenergic agonists (clonidine, pregabalin)

Surgical Pain Control

- direct delivery: implantable morphine pump
- central ablation: stereotactic thalamotomy, spinal tractotomy or dorsal root entry lesion
- peripheral ablation: nerve blocks, facet joint denervation
- deep brain stimulation (DBS) or dorsal column stimulation

Neuropathic Pain

Definition

- pain resulting from a disturbance of the central or peripheral nervous system

Symptoms and Signs

- hyperalgesia/allodynia
- subjectively described as – burning, heat/cold, pricking, electric shock, perception of swelling, numbness (i.e. stocking/sock distribution)
- can be spontaneous or stimulus evoked
- distribution may not fall along classical neuro-anatomical lines

Associated Issues

- sleep difficulty
- anxiety/stress/mood alteration
- sexual dysfunction

Causes of Neuropathic Pain

- peripheral neuropathy
 - systemic disease – diabetes, thyroid disease, renal disease, rheumatoid arthritis
 - nutritional/toxicity – alcoholism, pernicious anemia, chemotherapy
 - infectious – HIV
 - trauma – post surgical, nerve injury
- nerve root: post-herpetic neuralgia, cervical and lumbar radiculopathies, tic douloureux (see *Trigeminal Nerve*, N18), plexopathies
- central: MS, post-stroke, phantom limb, spinal cord injury
- Complex Regional Pain Syndromes (see N38)
- malignancy

Treatment

- **pharmacotherapy:** TCA, SNRI, anticonvulsant, long acting opiate, topical lidocaine, capsaicin cream, intrathecal opioid or clonidine, Botox, nerve block
- **surgical therapies:** dorsal column neurostimulator, DBS (thalamus)
- **other therapies:**
 - neuropsychiatry – cognitive behavioural therapy, psychotherapy
 - rehabilitation – physiotherapy
 - CAM – acupuncture, meditation, massage therapy, TCM

Tic Douloureux (Trigeminal Neuralgia)

- see *Trigeminal Nerve*, N18

Postherpetic Neuralgia (PHN)

Definition

- pain persisting beyond 3 months in the region of a cutaneous outbreak of herpes zoster

Etiology and Pathogenesis

- destruction of the sensory ganglion neurons (e.g. dorsal root, trigeminal, or geniculate ganglia) secondary to reactivation of herpes zoster infection

Epidemiology

- 10-15% of all patients with cutaneous herpes zoster
- >80% of herpes zoster infected patients >80 years old

Signs and Symptoms

- types of pain: constant deep ache or burning, intermittent spontaneous lancinating/jabbing pain, allodynia
- distribution: thoracic > trigeminal > cervical > lumbar > sacral

Treatment

- acute herpes zoster
 - early treatment with antiviral agents (acyclovir; longer-acting famciclovir and valaciclovir more effective) may prevent PHN in patients over 50 years
- PHN
 - medical: TCA, pregabalin, gabapentin, opiate, lidocaine patch, intrathecal methylprednisolone
 - surgical: spinal tractotomy, dorsal root entry zone lesion

Complex Regional Pain Syndromes (CRPS)

Definitions

- CRPS is a pain syndrome characterized by the following
 1. presence of an initiating noxious event
 2. continuing pain, allodynia, or hyperalgesia with pain disproportionate to inciting event
 3. evidence during the course of symptoms of edema, changes in skin blood flow, or abnormal vasomotor activity
 4. absence of conditions that would otherwise account for degree of pain and dysfunction

Classification

- CRPS type I (reflex sympathetic dystrophy): minor injuries of limb or lesions in remote body areas precede onset of symptoms
- CRPS type II (causalgia): injury of peripheral nerves precedes the onset of symptoms

Signs and Symptoms

- stage I (acute)
 - pain: burning or aching disproportionate to initial injury
 - autonomic: edema and temperature inequality
- stage II (dystrophic)
 - pain: constant and increased by stimulus to affected part
 - autonomic: osteoporosis, cool hyperhydrotic skin, hair loss, cracked/brittle nails
- stage III (atrophic)
 - pain: paroxysmal spread
 - autonomic: thin, shiny skin, thickened fascia with contractures, bony demineralization

Investigations

- diagnosis is clinical
- trial of differential neural blockade may be helpful

Treatment

- medical: phenoxybenzamine (sympatholytic)
- surgical: paravertebral sympathetic ganglion blockade

Thalamic Pain (Dejerine Roussy Syndrome)

Definition

- hypersensitivity to pain as a result of damage to the thalamus

Etiology and Pathogenesis

- injury to ventral posterolateral (VPL) and ventral posteromedial (VPM) nuclei of the thalamus
 - ischemic stroke
 - hypertensive vascular hemorrhage

Signs and Symptoms

- begins with hemianesthesia
- then persistent spontaneous burning contralateral to lesion
- altered response to light cutaneous and deep painful stimuli

Treatment

- medical: amitriptyline, anti-convulsants
- surgical: stereotactic thalamic stimulation (may increase sensory deficit)

Headache

Clinical Approach to Headaches

Investigations

- good history and physical to rule out serious causes of headache
 - important aspects of neurologic exam: LOC and MSE, pupils (symmetry), fundi (papilledema, retinal hemorrhages), pronator drift, meningismus, deep tendon reflexes and Babinski, gait
- indications for a CT
 - new-onset headache, worst headache of life, thunderclap headache, headache with worrisome symptoms (fever, meningismus, altered LOC, focal neurologic deficits, trauma, papilledema, morning headache)
- if CT is negative but suspicion of SAH or meningitis, perform a lumbar puncture

Table 21. Headaches – Primary

	Tension-Type	Migraine	Cluster
Prevalence	70%	12%	<1%
Age of Onset	15-40	10-30	20-40
Sex Bias	F > M	F > M	M > F
Family History	None	+++	+
Location	Bilateral frontal Nuccho-occipital	Unilateral > bilateral Fronto-temporal	Retroorbital
Duration	Minutes – days	Hours – days	10 min-2 hours
Onset/Course	Gradual; worse in PM	Gradual; worse in PM	Daily headache for weeks, months, nocturnal
Quality	Band-like; constant	Throbbing	Constant, aching, stabbing
Severity	Mild-moderate	Moderate-severe	Severe (wakes from sleep)
Provoking	Depression Anxiety Noise Hunger Sleep deprivation	Noise Light Straining Coughing Activity	Light EtOH
Palliating	Rest	Rest	Walking around
Associated Sx	No vomiting No photophobia	Nausea/vomiting Photo/phonophobia Aura	Red watery eye Nasal congestion or rhinorrhea Unilateral Horner's
Physical Signs	Muscle tension in scalp/neck	Muscle tension in scalp/neck Tender scalp arteries	Red watery eye, rhinorrhea Eyelid droop
Management	Non-pharmacological <ul style="list-style-type: none"> • Psychological counseling • Physical modalities (e.g. heat, massage) Pharmacological <ul style="list-style-type: none"> • Simple analgesics • Tricyclic antidepressants 	Acute Rx <ul style="list-style-type: none"> • ASA • NSAIDS • Triptans • Ergotamine Prophylaxis <ul style="list-style-type: none"> • Propranolol • TCA • Anticonvulsants 	Acute Rx <ul style="list-style-type: none"> • O₂ • Sumatriptan (nasal or injection) Prophylaxis <ul style="list-style-type: none"> • Verapamil • Lithium • Methysergide • Prednisolone

Table 22. Headaches – Serious

	Meningeal Irritation	Increased Intracranial Pressure	Temporal Arteritis
Incidence	<1%	<1%	<<1%
Age of Onset	Any age	Any age	>60
Sex Bias	No bias	No bias	No bias
Location	Generalized; stiff neck	Any location	Temporal
Duration	Variable	Chronic	Variable
Onset/Course	Meningitis: hours-days SAH: thunderclap onset	Gradual; worse in AM	Variable
Quality	Variable	Unlike any previous headache	Throbbing
Severity	Severe	Severe	Variable; can be severe

The Rational Clinical Examination: Does this Patient with Headache have a Migraine or Need Neuroimaging?

JAMA 2006; 296:1274-83

Does this patient with headache have a migraine?

The most useful panel of questions for diagnosing migraine is summarized by the POUNDing mnemonic:

- P** – Pulsatile quality
O – duration of 4-72 h/ours
U – Unilateral location
N – Nausea or vomiting
D – Disabling intensity

The LR for definite or possible migraine diagnosis varies with the number of features present: with ≥4, 3 and ≥2 features, the LRs are 24 (1.5-388), 3.5 (1.3-9.2) and 0.41 (0.32-0.52) respectively.

Does this patient with headache need neuroimaging?

The prevalence of significant intracranial pathology (pretest probability) varies by population. In those with chronic headache the prevalence is 1.2% (0.77-1.8%). In adult onset (>40 yrs) migraine-type headache the prevalence is 0.0% (0.0-5.3%).

However, in those presenting with new or changed headache the prevalence is 32% (24-42%), and in those presenting with thunderclap headache the prevalence is 43% (20-68%).

In these different populations, no clinical feature was found to be useful in ruling out significant intracranial pathology in a meaningful way.

However, several individual clinical features were found to be predictive of significant intracranial pathology:

cluster-type headache	10.7 (2.2-52)
abnormal neurological exam	5.3 (2.4-12)
undefined-type headache (non-tension/migraine/cluster-type)	3.8 (2.0-7.1)
headache with aura	3.2 (1.6-6.6)
aggravated by exertion/Valsalva	2.3 (1.4-3.8)
headache with vomiting	1.8 (1.2-2.6)



SSx of Serious Headaches Include:

1. The sudden onset of a severe headache;
2. Accompanying impaired mental status, fever, seizures, or focal neurologic deficits; or
3. New headaches beginning after age 50.

Table 22. Headaches – Serious (continued)

	Meningeal Irritation	Increased Intracranial Pressure	Temporal Arteritis
Provoking	Head movement	Lying down Valsalva Head low Exertion	
Palliating	Rest and immobility	Standing/sitting	
Associated Sx	Neck stiffness Photophobia Focal deficits (e.g. CN palsies)	Nausea/vomiting Focal neuro Sx Decreased level of consciousness	Polymyalgia rheumatica Jaw/tongue claudication Visual loss
Physical Signs	Kernig's sign Brudzinski's sign	Focal neuro Sx Papilledema	Temporal artery changes: • Firm, nodular, incompressible • Tender
Management	CT/LP	CT/MRI and treat appropriately See also <u>Neurosurgery</u> , NS5	Prednisone See also <u>Rheumatology</u> , RH17
Etiology	Meningitis, SAH	Tumour, IIH, malignant hypertension	Vasculitis (GCA)

SAH – subarachnoid hemorrhage; IIH – idiopathic intracranial hypertension; GCA – giant cell arteritis

**Structures Involved in Nociception of Headaches**

- Dura
- Large intracranial vessels
- CN V

Primary Headache disorders

- tension-type, migraine, cluster, ice pick, exertional

Headaches with serious risk to life or function

- subarachnoid hemorrhage (SAH), meningitis, herniation (from space-occupying lesion), temporal arteritis, venous sinus thrombosis

Secondary causes of headaches

- SAH, intracranial hemorrhage, stroke, meningitis/encephalitis, sinusitis, trauma, increased intracranial pressure (space-occupying lesion, malignant HTN or pseudotumour cerebri), post lumbar puncture, temporal arteritis, drugs/toxins (in particular analgesia-induced/medication overuse)

Migraine Headaches

Definition (common migraine)

- ≥5 attacks fulfilling each of the following criteria
 - 4-72 h duration
 - 2 of the following: unilateral, pulsating, moderate-severe (interferes with daily activity), aggravated by routine physical activity
 - 1 of the following: nausea/vomiting, photophobia/phonophobia/osmophobia

Epidemiology

- 18% females, 6% males; frequency decreases with age (especially at menopause)

Etiology and Pathophysiology

- neurovascular theory of migraines (controversial)
 - baseline state of neuron hyper-excitability
 - during migraine: wave of neuronal excitation followed by wave of depression
 - ♦ associated with vasoconstriction and dilation
 - initiating event may occur in brainstem
- trigger: stress, sleep excess/deprivation, drugs (estrogen, nitroglycerin), hormonal changes, caffeine withdrawal, chocolate, tyramines (e.g. red wine), nitrites (e.g. processed meats)
- auras are felt to be due to a wave of excitation/depression leading to the symptoms experienced in an aura (e.g. visual symptoms due to wave through occipital cortex)

Signs and Symptoms

- stages of uncomplicated migraine
 - prodrome (hours to days before headache onset)
 - aura
 - headache (see Table 21 for description of typical headache)
 - postdrome
- aura
 - fully reversible symptom of focal cerebral dysfunction lasting <60 minutes
 - examples:
 - ♦ homonymous visual disturbance (fortification spectra – zigzags; scintillating scotomata – spots)
 - ♦ unilateral paresthesiae and numbness or weakness
 - ♦ aphasia
- prodrome/postdrome: appetite change, autonomic symptoms, altered mood, psychomotor agitation/retardation



The oral contraceptive pill is contraindicated with complicated migraine due to risk of stroke.



Migraine auras can mimic other causes of transient neurological deficits (e.g. TIAs and seizures).

- classification of migraines
 - common migraine: no aura
 - classic migraine: with aura (headache follows reversible aura in 60min)
 - complicated migraine: with severe/persistent sensorimotor deficits
 - ♦ examples:
 - basilar-type migraine (occipital headache with diplopia, vertigo, ataxia, and altered level of consciousness)
 - hemiplegic/hemisensory migraine
 - ophthalmoplegic migraine
 - acephalgic migraine (aka migraine equivalent): aura without headache

Management

- avoid triggers
- mild to moderate migraine treatment
 - 1st line treatment: NSAIDS – ASA, ibuprofen, naproxen
- moderate to severe migraine treatment
 - triptans (most effective), ergots (dihydroergotamine, DHE), Tylenol® #3
- migraine prophylaxis: anticonvulsants (divalproex, topiramate), TCA (amitryptiline, nortriptyline), propranolol, 5HT antagonists (methylsergide), calcium channel blocker (verapamil)

Episodic Tension-Type Headache

Diagnostic Criteria

1. at least 10 previous headache episodes fulfilling criteria 2 through 4; number of days with such headaches: less than 180 days per year
2. headache lasting from 30 minutes to 7 days
3. at least two of the following pain characteristics:
 - a. nonpulsatile (tightening)
 - b. mild-moderate intensity
 - c. bilateral
 - d. not aggravated by normal routine
4. both of the following (or only one is present):
 - a. no nausea or vomiting
 - b. no photophobia or phonophobia

Chronic Tension-Type Headache

Diagnostic Criteria

1. average headache frequency of more than 15 days per month for more than 6 months fulfilling the following criteria
2. at least 2 of the following pain characteristics
 - a. pressing/tightening (nonpulsating) quality
 - b. mild or moderate intensity (may inhibit but does not prohibit activities)
 - c. bilateral location
 - d. no aggravation from climbing stairs or similar routine physical activity
3. both of the following
 - a. no vomiting
 - b. no more than one of the following: nausea, photophobia, or phonophobia
4. secondary headache types not suggested or confirmed

Cluster Headache

Diagnostic Criteria

1. at least five attacks fulfilling criteria 2 to 4 below
2. severe unilateral, supraorbital and/or temporal pain lasting 15 to 180 minutes (untreated)
3. headache associated with ipsilateral (to pain): conjunctival injection or lacrimation, nasal congestion or rhinorrhea, facial sweating, miosis or ptosis, eyelid edema, restlessness/agitation
4. not attributed to another disorder

Pharmacological Treatments for Acute Migraine

Pain 2002; 97:247-57

Study: Meta-analysis of 54 double-blind, placebo-controlled RCTs of pharmacologic treatment of acute migraine of moderate to severe intensity (21,022 patients in total).

Data extraction: Number of patients, dosing regimens, details of study design, and timing or type of rescue medication. Outcomes included headache relief at 1 and 2 hours, freedom from pain at 2 hours, sustained relief for 24 hours, and adverse effects within 24 hours.

Main Results: Data were available for 9 oral medications, 2 intranasal medications, and subcutaneous sumatriptan. For HA relief at 2h, all interventions were effective except Cafergot®, with NNTs ranging from 2.0 for sumatriptan 6mg s.c. to 5.4 for naratriptan 2.5 mg. The lowest NNT for oral medication was 2.6 for eletriptan 80 mg. For patients pain free at 2h, the lowest NNT was 2.1 for sumatriptan 6 mg s.c., with the lowest NNT for oral medication being 3.1 for Rizatriptan 10 mg. For sustained relief over 24h NNT ranged from 2.8 for eletriptan 80 mg to 8.3 for rizatriptan 5 mg. Side effects could not be analyzed systematically. There were no drug-to-drug comparisons.

Conclusion: Overall, most treatments were effective. Subcutaneous sumatriptan and oral triptans were most effective.



A prophylactic agent is recommended only if migraine attacks are severe enough to cause impairment of a patient's quality of life or if a patient has >3 migraines/month that have not responded adequately to treatment.

Source: Sliverstein SD et al. Practice parameter: Evidence-based guidelines for migraine headache (an evidence based review). *Neurology* 2000; 55:754-63



Cluster headaches can occur up to 8 attacks per day.

Sleep Disorders

Overview of Sleep



Sleep Regulators

1. Circadian rhythm: suprachiasmatic nucleus in hypothalamus
2. Sleep debt of 'somnogens' (possibly adenosine) that accumulates with time spent awake

Definition

- sleep is a reversible state of unresponsiveness and lack of perceptual awareness of the environment

Anatomy of Sleep

- the suprachiasmatic nucleus (SCN), located in the anterior hypothalamus, receives afferents from the retina and possibly from the lateral geniculate body; it projects not only to other hypothalamic nuclei, but also to the basal forebrain, thalamus, and periaqueductal gray

Sleep Stages

- **Stage 1:** 50% of alpha waves get replaced by theta waves (4-7 Hz), slow rolling eye movements, high muscle tone
- **Stage 2:** vertex K complexes, beta waves (>13 Hz), and high voltage (positive and negative) discharges with spindles on EEG; eye movement is still; high muscle tone
- **Stage 3 and 4 (Delta sleep):** slow wave (<2 Hz) but high voltage activity on EEG, still eye movements, low muscle tone, increased GH release, decrease in BP/HR/CO/RR
- **Rapid Eye Movement (REM) sleep:** mixed frequencies on EEG with low voltage and sawtooth waves, rapid eye movements, muscle paralysis, cholinergic brain state, dreaming

Disturbances of Alertness and Sleep

Coma

- see Neurosurgery, NS35

Insomnia

- **definition:** subjective complaint of poor sleep quality, non-restorative
- **categories**
 - sleep onset: difficulty falling asleep; rule out disordered breathing, restless leg syndrome, and anxiety
 - maintenance: waking up; rule out intrinsic sleep disorder with sleep study
 - sleep offset: early morning awakening; rule out depression or disordered breathing
 - non-restorative sleep
- **differential diagnosis**
 - primary insomnia
 - ♦ psychophysiologic hyperarousal from efforts to fall asleep
 - treatment: improve sleep hygiene
 - ♦ sleep state misperception: normal sleep demonstrated despite complaint of poor sleep
 - ♦ idiopathic insomnia
 - treatment: benzodiazepine receptor agonists or heterocyclic antidepressants
 - ♦ sleep apnea
 - obstructive sleep apnea: refer to Respirology, R32
 - central sleep apnea: no effort to breathe over 10 seconds
 - DDx: heart failure, syringobulbia, lateral medullary syndrome, brainstem dysfunction
 - ♦ restless leg syndrome (RLS) and periodic limb movement disorder (PLMD)
 - RLS: unpleasant sensations creeping along leg leads to need to move legs leading to problems with sleep initiation
 - PLMD: repetitive leg movements in sleep, 90% of RLS
 - DDx: spasticity, radiculopathy, neuropathy, pregnancy, alcohol, iron deficiency
 - treatment: iron supplement, dopamine agonist 1-2h prior to bed
 - secondary insomnia
 - ♦ poor sleep hygiene
 - ♦ transient situation: associated with major life change or stressful event
 - resolves on its own
 - ♦ secondary to psychiatric disorders (80% of psychiatric patients)
 - depression has been shown to be associated with short REM latency
 - ♦ secondary to neurologic disorders
 - examples: dementia, Parkinson's disease, hemiballism, Huntington's disease, atlantoaxial subluxation, myotonic dystrophy
 - ♦ secondary to drugs/toxins
 - examples: caffeine, alcohol, nicotine, amphetamines, cocaine, antidepressants, glucocorticoids, sedative (withdrawal of night), arsenic, copper, lead, mercury
 - ♦ fatal familial insomnia: rare degenerative prion disease of increasing sleep
 - onset insomnia leading to death within 7 to 13 months
 - associated symptoms: fever, excess salivation, sweating
 - ♦ others: environmental, altitude (lower FIO₂)



3 Categories of Dysomnias

1. Intrinsic sleep disorders
2. Extrinsic sleep disorders
3. Circadian related sleep disorders



Alcohol shortens sleep latency and promotes drowsiness, but leads to poor sleep maintenance during second half of sleep.

Narcolepsy

- irresistible desire to sleep in inappropriate circumstances and places
- **clinical features:** cataplexy, sleep paralysis (unable to move upon waking for 2-3 minutes), hypnagogic/hypnopompic hallucinations (vivid dreams or hallucinations at sleep onset or at awakening)
 - 10% of patients suffer all four symptoms ("narcolepsy/cataplexy tetrad")
- **epidemiology:** M>F, prevalence 1:2000, onset in adolescence/early adult
 - symptoms can become less troublesome with age but it is a life-long disorder
- **etiology:** post head injury, multiple sclerosis, hypothalamic tumours; rarely familial
- **diagnosis:** based on clinical history + EEG findings of REM in <15 min of sleep onset; seen on 2/4 naps during a multiple sleep latency test.
- **treatment**
 - lifestyle modification ("cat naps") can occasionally be effective management on their own; certain activities are restricted (e.g. driving)
 - modafinil (non-amphetamine stimulant)
 - ♦ amphetamines avoided because of their propensity for habituation
 - selegiline (metabolized in part to amphetamine), is a stimulant that also reduces cataplexy symptoms.
 - others: moxindol, pemoline, and clomipramine are also effective



Cataplexy: brief episodes of muscle paralysis in response to excess emotion (e.g. laughter).



Pathophysiology
Narcolepsy patients have decreased levels of hypocretin in CSF.

Parasomnias Associated with Slow Wave Sleep: Arousals

- occur in first 1/3 of sleep during stage 3 and 4
- arousals associated with confusion/disorientation, amnesia
- treatment: self-limiting, diazepam
- **confusional arousals/sleep drunkenness:** partial arousal from slow wave sleep associated with confusion and startling, resistance to being consoled, and appearance of being awake
 - aggravated by napping in narcolepsy, stress/anxiety, fever, excess exercise, night terror
 - predominantly in children
- **somnambulism:** sleep walking (ranges from sitting up in bed to violent sleep behaviour)
 - 1-15% of population, with greatest frequency in childhood
 - clinical presentation: agitation, automatisms, walking/running, completion of complex tasks, verbalization, ± open eyes, choreiform movements, enuresis, difficult to arouse
 - associated with fever, sleep deprivation, sleep apnea, urinary retention, external noise, medications
 - increases the risk of psychoneurosis in adults, but not in children.
- **night terror:** abrupt awakening associated with fear and autonomic stimulation
 - in children (ages 2 to 4), resolves by adolescence
 - clinical presentation: child awakes suddenly, sits up in bed and screams, eyes open, dilated pupils, sympathetic activity, increased muscle tone, child is not consolable, agitation, vocalizations, enuresis
 - different from other slow wave sleep arousals, night terrors can occur at any time of the night
 - associated with fever, bladder distention, sleep deprivation, medications



Slow wave sleep arousal is associated with confusion and amnesia; REM sleep arousal is associated with rapid awakening and vivid dream recall.

Circadian Abnormalities

- **familial advanced sleep phase syndrome**
 - autosomal dominant condition of early morning awakening (i.e. "morning larks")
 - pathophysiology: codon mutation of Per gene leads to a 4 hours advance of sleep, temperature and melatonin rhythms
- **shift work sleep disorder:** due to sleeping at times different than normal circadian rhythm
- **delayed sleep phase syndrome:** body's circadian rhythm is delayed compared to time displayed on clock
- **time zone change syndrome** (jet lag)

REM Sleep Behaviour Disorder

- pathophysiology: loss of spinal inhibition that normally occurs in REM sleep leading to hyperpolarization of ventrolateral reticulospinal tract motor neurons of spinal cord
- diagnostic criteria (American Sleep Disorder Association): diagnosis requires at least #2 and 3 are fulfilled
 1. injurious behaviour during sleep
 2. movement associated with dreaming state
 3. at least 1 of:
 - ♦ potentially harmful behaviours in sleep
 - ♦ acting out dreams
 - ♦ disruption of sleep due to activities
 4. polysomnograph shows:
 - ♦ excess chin tone on EMG and/or excess chin or limb twitching on EMG
 - ♦ 1 of: excess limb/body jerking, injurious behaviours, no epileptic activity
- rule out psychiatric or other sleep disorders

Medical Disorder Affecting Sleep

- nocturnal leg cramps: DM, exercise, pregnancy, metabolic, endocrine, Parkinson's disease, arthritis
- mood disorders
- alcohol abuse
- cerebral degenerative disorders
- trauma
- dementia: insomnia associated with wandering, aggression, verbalization, delirium during early evening ("sundowning")
- Parkinsonism: sleep onset and sleep maintenance insomnia
- sleep related epilepsy: brain synchronization is increased during sleep leading to an increased frequency of seizures during sleep, especially during non-REM sleep
 - triggers: sleep deprivation
 - treatment of sleep disorders decreases seizures, and treatment of epilepsy improves sleep
- asthma/COPD: lower airway obstruction, coughing, wheezing and SOB can interrupt sleep
- GERD
- fibromyalgia: associated with pain, nonrefreshing sleep, fatigue, muscle tenderness and trigger points

CNS Infections

- see [Infectious Diseases](#), ID6

Spinal Cord Syndromes

- see [Neurosurgery](#), NS28

Stroke

Terminology

- **Stroke:** sudden onset neurological deficits of a vascular basis lasting longer than 24 hours
- **Transient Ischemic Attack (TIA):** sudden onset neurological deficits of a vascular basis that resolve after a brief period (usually <30 min)
- **Reversible Ischemic Neurological Deficit (RIND or minor stroke):** sudden onset neurological deficits of a vascular basis lasting >24 hours that resolve completely or near completely within days
- **Stroke in evolution or progressing stroke:** stroke that is actively progressing due to propagation of underlying vascular etiology to include further vascular territory over hours

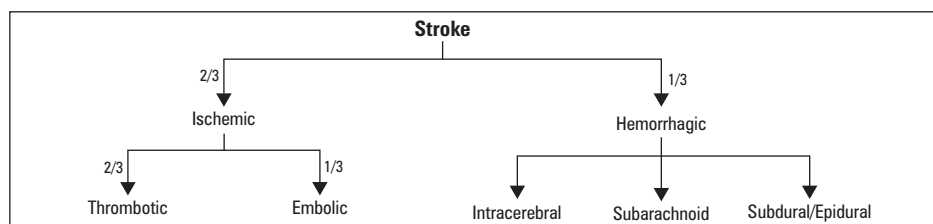


Figure 22. Classification of Stroke

Approach to Stroke

- **Initial Assessment Goals**
 1. Has the patient had a stroke?
 2. Is the patient a candidate for tPA?
- **Onset:** time when last known to be awake and symptoms free
- **Mimics to rule out:** post-ictal, hypoglycemia, systemic infection, tumours, conversion disorder

Assessment

- NIH Stroke Scale (NIHSS – see sidebar)
 - applies mainly to MCA territory
- CT signs of acute stroke
 - loss of cortical white-grey differentiation
 - sulcal effacement (i.e. mass effect decreases sulci)
 - hypodensity of parenchyma
 - insular ribbon sign
 - hyperdense MCA sign
- ASPECT score: where 10/10 is normal and <4/10 signifies high risk of bleed with tPA
 - subtract 1 point for each of following structures if abnormal within the ischemic hemisphere: caudate, lentiform, insula, internal capsule, MCA 1, 2, 3, 4, 5, 6

Treatment

- if no hemorrhage on CT and there is a clinical indication, tPA may be offered to the patient within the appropriate time limits (see [Emergency Medicine](#), ER38 for more tPA details)



The **National Institute of Health Stroke Scale (NIHSS)** is a standardized clinical examination that determines the severity of an acute stroke. It can also be used to monitor response to treatment over time.

The scale uses 11 items that evaluate:

- 1) Level of consciousness
- 2) Visual system
- 3) Motor system
- 4) Sensory system
- 5) Language abilities

Scoring (x/42):

0=no stroke

1-4=mild stroke

5-15=moderate stroke

15-20=moderate to severe stroke

21-42=severe stroke

tPA should be considered if score 6 or greater.

Stroke Syndromes

**Stroke Syndromes According to Vascular Territory**

- **ACA:** contralateral paresis and sensory loss, loss of bladder control (hypertonic detrusor)
- **MCA:** proximal occlusion involves all of the below findings
 - superior division: contralateral face and arm paresis and sensory loss, Broca's (expressive) aphasia (if in dominant hemisphere)
 - inferior division: contralateral homonymous hemianopsia (esp. inferiorly), contralateral agraphesthesia and astereognosis, anosognosia, contralateral neglect, Wernicke's (receptive) aphasia (if in dominant hemisphere)
- **Internal carotid:** premonitory TIA or transient monocular blindness (amaurosis fugax), asymptomatic or similar to MCA occlusion
- **PCA:** contralateral homonymous hemianopsia (especially superiorly), midbrain findings (vertical gaze palsy, CN III palsy, INO), occipital findings (anomia, alexia without agraphia, visual agnosia)
 - if bilateral: cortical blindness or prosopagnosia
- **Basilar artery**
 - proximal (usually thrombosis) occlusion: CN VI palsy, impaired horizontal EOM impairment, vertical nystagmus, reactive myosis, hemi- or quadriplegia, coma, locked-in syndrome
 - distal (usually embolic) occlusion (aka Top of the Basilar Syndrome): decreased LOC, CN III palsy, decerebrate or decorticate posturing
- **PICA (Lateral Medullary or Wallenberg Syndrome):** ipsilateral ataxia, ipsilateral Horner's, ipsilateral facial sensory loss, contralateral limb impairment of pain and temperature, nystagmus, vertigo, N/V, dysphagia, dysarthria, hiccup
- **Lacunar Infarcts (basal ganglia, thalamus, posterior limb internal capsule)**
 - pure motor hemiparesis: contralateral arm, leg, and face
 - pure sensory loss: hemisensory loss (usually thalamic)
 - ataxic hemiparesis: ipsilateral ataxia and leg paresis
 - dysarthria-clumsy hand syndrome: dysarthria, facial weakness, dysphagia, mild hand weakness and clumsiness



Cerebral venous sinus thrombosis should be considered in the differential diagnosis of stroke and headache. It is an uncommon cause of either, but is associated with high morbidity and mortality. Patients often present with headache alone, but can also have seizures, focal neurological deficits, or cranial nerve palsies. MRI with gadolinium is the best diagnostic test. Treatment is typically anticoagulation with heparin initially, then transition to warfarin.

Ischemic Stroke

Etiology

- **thrombosis:** stepwise deficits, preceded by TIAs
- **embolus:** abrupt onset, no warning TIA, maximal at onset, multifocal if cardiac origin, seizure more likely

Conditions Associated with Increased Risk of Cerebral Ischemia

- **vascular disorders:** atherosclerosis, vasculitis, SLE, syphilis, AIDS, carotid or vertebral dissection, drug abuse (cocaine, amphetamines, heroin), migraines, venous or sinus thrombosis, lacunar infarcts (due to chronic HTN)
- **cardiac disorders:** mural thrombus, rheumatic heart disease, arrhythmia, endocarditis, mitral valve prolapse, prosthetic heart valves
- **hematologic disorders:** thrombocytosis, polycythemia, sickle cell disease, leukocytosis, hypercoagulable states



If possibility of cardioembolic source, look for arrhythmias like atrial fibrillation.

**Causes of ICH**

HTN, trauma, AVM, hemorrhage in cerebral infarcts, drug abuse, cerebral amyloid angiopathy, tumours, coagulopathies, anticoagulation.

**Subclavian Steal Syndrome**

Vertebrobasilar insufficiency due to subclavian stenosis associated with left arm use causing vertigo, headaches, left arm claudication.



The classic site of hypertensive hemorrhages is the basal ganglia.

t-PA in Acute Stroke – NINDS Trial

NEJM 1995; 333:1581-7

Study: Randomized, double-blind, placebo-controlled trial (3 month follow-up).

Patients: 624 patients (mean age 76 y, 58% men, 65% white) with ischemic stroke of recent onset, and no evidence of intracranial hemorrhage on CT. Exclusions included hx of recent stroke or recent surgery, SBP=185, DBP=110, symptoms of SAH, recent GI or GU hemorrhage, seizure with onset of stroke, and recent use of anticoagulants.

Intervention: IV t-PA (0.9 mg/kg) or placebo within 180 minutes of the onset of symptoms.

Main outcomes: Neurologic deficit at 24 hours (NIHSS scale) and functional outcome at 3 months (composite score).

Results: There was no significant difference between groups at 24 hours. At 3 months, there were more patients in the t-PA group with minimal or no disability (50% vs. 38%, $p=0.03$). Intracerebral hemorrhage was more common in the t-PA group ($p<0.001$). There was no significant difference in mortality.

Conclusion: IV t-PA given within 3 hours of onset of acute ischemic stroke improves functional outcome at 3 months. The risk of intracerebral bleeding is increased.

Addendum: When re-assessed at 12 months from the time of treatment, patients in the t-PA group were 30% more likely to have minimal or no disability, with no significant difference in mortality or rate of recurrent stroke (*NEJM* 1999; 340:1781-7).

Hemorrhagic Stroke

Etiology

- **intracerebral (ICH):** hypertensive, amyloid angiopathy, or other cause
- **subarachnoid (SAH):** aneurysm, AVM, or other cause
- **epidural/subdural hematoma**

Investigations

- bloodwork: CBC, ESR, VDRL, serum glucose, cholesterol and lipids
- ECG
- CT \pm MRI
- lumbar puncture (rule out subarachnoid hemorrhage)
- intrarterial angiography or MRA (anterior circulation TIAs or dissection)
- carotid doppler or transcranial doppler
- echocardiography

Hypertensive Stroke

Etiology

- BP above upper limit of autoregulation of cerebral blood flow (normal is 150-200 mmHg), chronic HTN, acute HTN
- chronic HTN stimulates cerebral blood vessels causing adaptive changes like hyalinization and lipodosis to preserve the blood-brain barrier. This process affects mainly smaller penetrating arteries (<200 mm in diameter) leading to lacunar infarcts of the basal ganglia and thalamus
- acute HTN can cause hypertensive encephalopathy with $\text{dBP} > 130$ or $\text{sBP} > 200$ assoc with findings on fundoscopy, focal neural Sx, N/V, visual disturbances and change in LOC due to microinfarctions and petechial hemorrhages
- pathology: hemorrhages occur from rupture of damaged blood vessels, likely at the site of Charcot-Bouchard aneurysms
- most common sites: putamen, thalamus, cerebellum, and pons

Treatment

- surgical: decompression to prevent herniation if cerebellar hematoma or superficial hemorrhage of cerebral white matter
- medical (controversial): antihypertensive to lower dBP to ~ 100 mmHg (typically nitroglycerin or furosemide used cautiously), corticosteroids for vasogenic edema

Global Cerebral Ischemia

- etiology: inadequate blood flow to brain to meet metabolic demands (e.g. cardiac arrest)
- when hypotension is less severe, the areas of the brain most severely affected are the watershed areas between ACA, MCA and PCA

Treatment of Stroke

A. ACUTE STROKE MANAGEMENT**Goals**

- ensure medical stability
- limit or prevent neuronal death

Practical Guidelines

- **general**
 - ABC's, check glucose, urgent CT to rule out hemorrhage and assess infarct
 - other labs and tests: CBC, PTT, INR, ECG
- **diagnosis**
 - make the correct etiological diagnosis so you have a rational approach for secondary prevention of stroke
 - consider transfer to stroke centre for neuroprotective or thrombolytic therapy if the patient is seen in first few hours (have been proven effective in clinical tests)

Thrombolysis

- rt-PA (recombinant tissue plasminogen activator) within 3 hours of acute ischemic stroke onset (NINDS trial)
 - treated patients were 30% more likely to have minimal or no disability at 3 months
 - 6.4% of patients had a symptomatic intracerebral hemorrhage (0.6% in placebo group)
 - treatment did not affect mortality compared to placebo but patients with severe strokes were more likely to have favourable outcomes if treated with rt-PA, benefits of rt-PA were sustained at 12 months

Anti-Platelet Therapy

- give ASA at presentation
- give antiplatelet agents if ASA not suitable or if already taking ASA
 - clopidogrel (75 mg daily)
 - ASA + dipyridamole (Aggrenox®)

Table 23. Treatment

Condition		Antiplatelet	Anticoagulation	Thrombolytic	Endarterectomy
Carotid Stenosis		+	-	-	±
TIA	Cardiac	±	+	-	-
	Carotid or vertebrobasilar	+	±	-	+ (carotid)
Stroke-in-evolution		-	±	-	-
Stroke	Cardiac	±	+	-	-
	Carotid or vertebrobasilar	+	±	+	+ (carotid)

- **Antiplatelet:** ASA, dipyridamole, ticlopidine, clopidogrel
- **Anticoagulation:** Heparin IV to appropriate target level then warfarin to INR 2-3
- **Thrombolytic:** 1h IV infusion of recombinant tissue plasminogen activator (rt-PA) for ischemic stroke within 3h of stroke onset. Get 24h CT to R/O ICH. Also option of intra-arterial tPA for specific clinical situations
- **Carotid Endarterectomy:** if 50-99% stenosis with low risk of perioperative death or disabling stroke

Blood Pressure Control

- do not lower the blood pressure unless the hypertension is severe
 - antihypertensive therapy is withheld for at least 5 days after thromboembolic stroke unless there is acute MI, renal failure, aortic dissection, sBP above 220 mmHg, or dBP above 120 mmHg
- acutely elevated BP is necessary to maintain brain perfusion
- most patients with an acute cerebral infarct are initially hypertensive and their BP will fall spontaneously within 1-2 days
- IV labetalol is usually first line if needed

Blood Sugar

- avoid hyperglycemia which will increase the infarct size

B. OTHER MANAGEMENT ISSUES

- prevent complications
 - NPO if swallowing difficulty
 - DVT prophylaxis if limb weakness
 - initiate rehabilitation
- therapy (see also *Primary and Secondary Prevention* below)
 - determine the vascular territory and etiology, then treat accordingly
- lower temperature if febrile

Primary and Secondary Prevention

Carotid Territory Event

- carotid endarterectomy benefits those with symptomatic severe stenosis (70-99%), and is less beneficial for those with symptomatic moderate stenosis (50-69%), see [Neurosurgery](#), NS21

Asymptomatic Carotid Bruit

- suggests the presence of atherosclerotic stenosis and signifies increased risk for both cerebral and myocardial infarction
- modify risk factors, ± antiplatelet therapy
- if stenosis >60%, risk of stroke is 2% per year; carotid endarterectomy reduces the risk of stroke by 1% per year (but 5% risk of complications)

Hypertension

- primary prevention
 - antihypertensives reduce the risk of ischemic stroke in elderly patient with isolated systolic hypertension (SHEP trial)
 - ♦ ramipril 10 mg OD is effective in patients at high risk for cardiovascular disease (HOPE-Stroke trial)
 - ♦ ACEI reduce the risk of stroke beyond their antihypertensive effect
- secondary prevention
 - ACEI and thiazide diuretics are useful in patients with a Hx of stroke/TIA (PROGRESS trial)



Absolute Contraindications to tPA

Improving Sx, minor Sx, hemorrhage or mass on CT, high INR or aPTT, seizure at stroke onset, recent major surgery or trauma, recent GI or urinary hemorrhage, recent LP or arterial puncture at noncompressible site, sBP >185, dBP >110, aggressive Rx to decrease BP, uncontrolled serum glucose, thrombocytopenia, PMH ICH, Sx of SAH/pericarditis/MI, pregnant.



Relative contraindications to tPA

Early signs of large cerebral infarction, NIHSS >22, resistant HTN, age >85, Hx AVM or aneurysm.



50% of ICH due to tPA are fatal!



BP **must** be lowered to sBP <185 and dBP <110 before tPA is given.

Aspirin and Heparin in Acute Stroke – International Stroke Trial

Lancet 1997; 349:1569-81

Study: Randomized, open trial with 6 month follow-up.

Patients: 19,435 patients (54% men) with suspected acute ischemic stroke of recent onset (less than 48 h), with no evidence of intracranial hemorrhage, and no clear indications for, or contraindications to, heparin or aspirin. Intervention: Half the patients were allocated unfractionated heparin (5000 or 12,500 IU bid), and half were never allocated heparin; Similarly, half were allocated aspirin 300 mg daily. Thus patients were randomly assigned to receive aspirin, heparin, both, or neither.

Outcomes: Death within two weeks, and death or dependency at 6 months.

Results: For both heparin vs. no heparin and aspirin vs. no aspirin, there was no significant difference in death at 2 weeks, or death or dependency at 6 months. Both aspirin and heparin-allocated patients had significantly fewer recurrent ischaemic strokes within 14 days, but this benefit was completely offset by a similar-sized increase in hemorrhagic stroke in those receiving heparin. After adjustment for predicted prognosis, the aspirin group showed a decreased risk of death or dependence at 6 months (14 per 1000 fewer, p=0.03).

Conclusion: The IST suggests that aspirin should be started immediately after the onset of ischemic stroke.

ACE Inhibitor in Stroke Prevention – HOPE Trial
NEJM 2000; 342:145-53

Study: Randomized, blinded, placebo-controlled trial. Mean follow-up 5 years.

Patients: 9297 patients 55 years of age or older (mean age 66 y, 73% men) who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure.

Intervention: Ramipril 10 mg once daily orally vs. matching placebo.

Main Outcomes: Stroke, myocardial infarction, or death from cardiovascular causes

Results:

Outcome	RRR (95%CI)	NNT (CI)
Stroke	32% (16 to 44)	67 (43 to 145)
MI, stroke, or CV mortality	22% (14 to 30)	26 (19 to 43)
All-cause mortality	16% (5 to 25)	56 (32 to 195)

Treatment with ramipril reduced the risk of stroke (3.4 percent vs. 4.9 percent; RR 0.68; $p < 0.001$).

Conclusion: In adults at high risk for cardiovascular events, ramipril reduced the risk of stroke, as well as other vascular events and overall mortality.

Statins in Stroke Prevention – MRC/BHF Heart Protection Study
Lancet 2002; 360:7-22

Study: Randomized, double-blind, placebo-controlled trial with mean follow-up of 5 years.

Patients: 20 536 patients aged 40 to 80 years (28% ≥ 70 y of age, 75% men) with nonfasting total cholesterol ≥ 3.5 mmol/L, who were considered to be at substantial 5-year risk of death from coronary heart disease because of cardiovascular disease, diabetes, or treated hypertension. 16% of patients had known cerebrovascular disease. Exclusions included chronic liver disease, evidence of abnormal liver or kidney function, muscle disease, and others.

Intervention: Run-in treatment involved 4 weeks of placebo followed by 4-6 weeks of a fixed dose of 40 mg simvastatin daily. Patients were then randomized to simvastatin 40 mg/d or placebo.

Main Outcomes: Included all-cause and vascular mortality, major coronary events, and stroke.

Results:

Outcome	RRR (95%CI)	NNT (CI)
Stroke	25% (15 to 34)	73 (51 to 131)
Major coronary event	27% (21 to 33)	33 (26 to 46)
All-cause mortality	13% (6 to 19)	58 (37 to 128)

Conclusion: Simvastatin safely reduced the risk of stroke, major coronary events, and all-cause mortality in patients at significant 5 year risk of coronary heart disease.

Organized Inpatient (Stroke Unit) Care for Stroke (Stroke Unit Trialists' Collaboration)

The Cochrane Database of Systematic Reviews 2001; Issue 3

Purpose: Assess the effect of stroke unit care compared with other models of care.

Study Characteristics: 23 trials, randomized (14) or quasi-randomized studies (9) involving 4911 patients.

Participants: Patients admitted to hospital who had suffered a stroke, defined as a focal neurological deficit due to cerebrovascular disease, excluding subarachnoid hemorrhage and subdural hematoma.

Intervention: Organised inpatient stroke unit care with multidisciplinary teams that exclusively manage stroke patients in a dedicated ward, with a mobile team, or within a generic disability service, compared with alternative forms of care, usually a general medical ward.

Primary Outcomes: Death, dependency (require assistance for basic activities of daily living), and the requirement for institutional care at the end of follow-up.

Results: The NNT to prevent one death is 33 (95% CI, 20-100), to prevent one patient being unable to live at home was 20 (95% CI, 12-50), and to prevent one patient failing to regain independence was 20 (95% CI, 12-50).

Conclusions: Acute stroke patients cared for in an organized stroke unit with a multidisciplinary care team are more likely to survive their stroke, return home and make a good recovery.

Anti-Platelet Therapy

- primary prevention
 - current evidence has not firmly established a protective role for antiplatelet agents for low-risk patients without a prior stroke/TIA
- secondary prevention
 - generally ASA is chosen as the initial antiplatelet of choice for stroke prevention
 - other agents (ASA + dipyridamole; clopidogrel) are reserved for those who suffer cerebrovascular symptoms while on ASA
 - warfarin is generally reserved for specific indications in stroke prevention, dissection, cardiac/atrial fibrillation, venous thrombosis

Hypercholesterolemia

- primary prevention
 - statins reduce the risk of stroke in patients with CAD or at high risk for cardiovascular events, even with normal cholesterol (CARE study)
- secondary prevention
 - more evidence is needed for high-risk patients with symptomatic cerebrovascular disease, but statins are generally used in these patients as well

Atrial Fibrillation

- primary and secondary prevention
 - warfarin is the first-line agent

Smoking

- primary prevention
 - smoking increases risk of stroke in a dose-dependent manner
- secondary prevention
 - after smoking cessation, the risk of stroke decreases to baseline within 2-5 years

Physical Activity

- regular physical activity is an important lifestyle measure in stroke prevention and this effect has a dose-response in terms of both intensity and duration of activity

Stroke Rehabilitation

- individualized based on severity and nature of impairment, may require inpatient program and continuation through home care or outpatient services
- multidisciplinary approach includes
 - dysphagia assessment and dietary modifications
 - communication rehabilitation
 - cognitive and psychological assessments including screen for depression
 - therapeutic exercise programs
 - assessment of ambulation and evaluation of need for assistive devices, splints or bracing
 - vocational rehabilitation

Multiple Sclerosis (MS)

Definition

- **Multiple Sclerosis:** a chronic inflammatory disease of the CNS characterized by relapsing remitting, or progressive, neurologic symptoms due to demyelination and early relative sparing of axons

Clinical Patterns of MS (Figure 23)

- relapsing remitting (RRMS) 85%, primary progressive (PPMS) 10%, progressive relapsing (PRMS) 5%, secondary progressive (SPMS)
- RRMS can become SPMS

MS Variants

- **Devic's = Neuromyelitis optica (NMO):** severe optic neuritis and extensive transverse myelitis extending >3 vertebral segments
- **Benign MS:** RR without major disability by 10 years
- **Clinically Isolated Syndrome (CIS):** single MS-like episode
- **Clinically Absent MS:** MRI disease only
- **Tumefactive MS:** solitary lesion >2 cm mimicking neoplasms on MRI
- **Fulminant MS (Marburg):** rapidly progressive and fatal MS associated with severe axonal damage, inflammation, and necrosis
- **Acute Disseminated Encephalomyelitis (ADEM):** monophasic demyelinating disorder with multifocal neurologic symptoms seen mainly in children often following infection or vaccination

Etiology

- genetic
 - polygenetic: the HLA-DR2 gene has been demonstrated to be a genetically susceptible area. 30% concordance for monozygotic twins, 2-4% risk in offspring of affected mother or father
- environmental
 - MS is more common in region with less sun exposure and thus lower stores of vitamin D
 - MS has also been linked to certain viruses, in particular an association with EBV has been found

Epidemiology

- onset 17-35, 3F:1M, except PPMS occurs in an older population with 1F:1M

Diagnosis

- Dissemination in Space and in Time as based on the revised McDonald criteria
 - Dissemination in Time: 2 or more attacks, new gadolinium enhancing lesion 3 months later, or new T2 lesions >1 month after first attack
 - Dissemination in Space: clinical evidence of 2 or more lesions; or three of [1 gadolinium enhancing or 9 T2 lesions], [1 infratentorial lesion], [1 juxtacortical lesion], [3 periventricular lesions]

Features

- symptoms in order of frequency: fatigue, depression, numbness, weakness, visual disturbance, bladder dysfunction, spasticity, impaired gait, cognitive disturbance, pain
- Lhermitte's sign: flexion of neck causes electric shock sensation down back into limbs indicating cervical cord lesion
- Uhthoff's phenomenon: worsening of symptoms (classically optic neuritis) in heat
- SPMS: classically weakness of legs in pyramidal distribution paired with cerebellar findings of arm (i.e. intention tremor)
- symptoms not commonly found in MS: visual field defects, aphasia, apraxia, progressive hemiparesis

Investigations

- **MRI:** demyelinating plaques appear as hyperintense lesions on T2 weighted MRI, with active lesions showing enhancement with gadolinium
 - typical locations: periventricular, corpus callosum, cerebellar peduncles, brainstem, juxta cortical region, and dorsolateral spinal cord
 - Dawson's fingers: periventricular lesions extending superiorly into corpus callosum
- **CSF:** oligoclonal bands in 90%, increased IgG concentration
- **evoked potentials (visual/auditory/somatosensory):** delayed but well-preserved wave forms

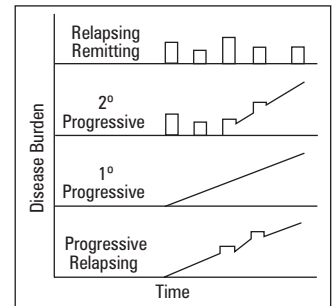


Figure 23. Clinical Patterns of MS



Most symptoms in MS are due to cord, brainstem and optic nerve lesions.

Recombinant Interferon Beta or Glatiramer Acetate for Delaying Conversion of the First Demyelinating Event to Multiple Sclerosis
Cochrane Database Syst Rev 2008; 2:CD005278.

Study: Cochrane systematic review. 2 RCT and quasi-RCT, double-blinded trials.

Population: 1160 patients with first neurological event suggestive of demyelination with positive brain MRI (clinically isolated syndromes, CIS).

Intervention: Either interferon beta (IFN β) versus placebo. (No appropriate glatiramer acetate trials were found).

Primary Outcomes: Proportion of patients converting to clinically definite MS, and adverse effects.

Results: A pooled odds ratio (OR) of 0.53 (5% CI, 0.40-0.71, $p < 0.0001$) for patients on IFN versus placebo at one year. Two year follow-up odds ratio was 0.52 (95% CI, 0.38-0.70, $p < 0.0001$). There was no significant increase in adverse events for those on IFN.

Conclusions: IFN β treatment can delay progression to clinically definite MS in patients with CIS in a two-year timeframe.

Treatment

- **acute treatment:** methylprednisolone 500-1000 mg IV daily X 3-7 days \pm taper
- **disease modifying therapy (DMT):** interferon-beta (Betaseron[®], Avonex[®], Rebif[®]), glatiramer acetate (Copaxone[®]) and natalizumab (Tysabri[®])
 - CIS: early treatment with Avonex may delay potential second attack
 - RRMS: DMT reduces rate of relapse by 30%; attacks shorter and less severe
 - SPMS: interferon-beta may slow progression
 - PPMS: immunosuppressant therapy (e.g. Methotrexate[®])
- **symptomatic treatment**
 - spasticity: baclofen, tizanidine, dantrolene, benzodiazepine
 - bladder dysfunction: oxybutynin
 - pain: TCA, carbamazepine, gabapentin
 - fatigue: amantidine, modafinil, methylphenidate
- **education and counseling:** MS society, support groups, psychosocial issues

Prognosis

- good prognostic indicators: female, young, RRMS, presenting with optic neuritis, low burden of disease on initial MRI, low rate of relapse early in disease
- PPMS: poor prognosis, higher rates of disability, poor response to therapy

Common Medications

Table 24. Common Medications

Mechanism of Action/Class	Generic Name	Trade Name	Dosing	Indications	Contraindications	Side Effects
Dopamine precursor	levodopa + carbidopa	Sinemet®	Carbidopa 25 mg/levodopa 100 mg PO tid Maximum 200 mg carbidopa and 2000 mg levodopa per day	Parkinson's Disease	Narrow-angle glaucoma, use of MAO inhibitor	Nausea, hypotension, hallucinations, dyskinesias in last 14 days, history of melanoma or undiagnosed skin lesions
Dopamine agonist	bromocriptine	Parlodel®	1.25 mg PO bid, increase by 2.5 mg/d q2-4wks, up to 10-30 mg PO tid	Parkinson's Disease	Concomitant use of potent inhibitors of CYP3A4, uncontrolled hypertension, ischemic heart disease, peripheral vascular disease. Caution with renal or hepatic disease	Hypotension, nausea, dizziness, constipation, diarrhea, vomiting, abdominal cramps, headache, nasal congestion, drowsiness, hallucinations
MAO B inhibitor	selegiline	Eldepryl®	5 mg PO bid	Parkinson's Disease	Concomitant use of meperidine or tricyclic antidepressants	Headache, insomnia, dizziness, nausea, dry mouth, hallucinations, confusion, orthostatic hypotension, increased akinesia, risk of hypertensive crisis with tyramine-containing foods
MAO B inhibitor	pyridostigmine	Mestinon®	600 mg/d PO divided in 5-6 doses Range 60-1500 mg/d	Myasthenia Gravis	GI or GU obstruction	Nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis, diaphoresis, muscle cramps, fasciculations, muscle weakness
Triptan	sumatriptan	Imitrex®	25-100 mg PO pm, maximum 200 mg/d	Migraine	Hemiplegic/basilar migraine, ischemic heart disease; cerebrovascular disease, uncontrolled hypertension, use of ergotamine/5-HT ₁ agonist in past 24 hours, use of MAO inhibitor in last 14 days, severe hepatic disease	Dizziness, sensation of heat, hypertensive crisis, disease, peripheral vascular disease, coronary artery vasospasm, cardiac arrest, nausea, vomiting, headache, hyposalivation, drowsiness
Ergot	dihydroergotamine	Migranal®	Nasal spray 0.5 mg/spray, maximum 4 sprays/day	Migraine	Hemiplegic/basilar migraine, high-dose ASA therapy, uncontrolled hypertension, ischemic heart disease, peripheral vascular disease, severe hepatic or renal dysfunction, use of triptans in last 24 hours; use of MAO inhibitors in last 14 days	Coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, ventricular fibrillation. May cause significant rebound headache
Anticonvulsant	carbamazepine	Tegretol® (Carbatrol, Epitol in USA)	Start at 100-200 mg PO OD-bid, increase by 200 mg/d up to 800-1200 mg/d (individual doses) if needed	Epilepsy – partial ± 2° generalization; generalized tonic-clonic	History of bone marrow depression, hepatic disease, hypersensitivity to the drug, or known sensitivity to tricyclic compounds such as amitriptyline	CNS disturbances (drowsiness, headache, unsteadiness, dizziness), nausea/vomiting, skin rash, agranulocytosis/aplastic anemia (rare)
Cholinesterase Inhibitor	donepezil	Aricept®	5 mg PO OD, may increase to 10mg PO OD after 4-6 weeks	Mild to moderate Alzheimer's Disease, Lewy Body Disease	Hypersensitivity to donepezil or to piperidine derivatives	Nausea, vomiting, diarrhea, insomnia, muscle cramps, fatigue, and anorexia
Immunomodulator	interferon beta-1b	Betaseron®	0.25 mg (8 MU) SC every other day	Relapsing-Remitting and Secondary Progressive Multiple Sclerosis	Pregnancy, hypersensitivity to natural or recombinant interferon beta	Injection site reactions, injection site necrosis, flu-like symptoms (fever, chills, myalgia) tend to decrease over time
Muscle Relaxant – Antispastic	baclofen	Lioresal®	Up to 20 mg PO qid, variable for intrathecal route	Spasticity (i.e. MS)	Hypersensitivity to baclofen (Spinal Cord Injury)	Transient drowsiness, daytime sedation, dizziness, weakness, fatigue, convulsions, hypotonia, hypersensitivity to donepezil or to piperidine derivatives
Antispasmodic – Anticholinergic	oxybutynin chloride	Ditropan®	5 mg PO bid	Uninhibited neurogenic bladder or reflex neurogenic bladder	Glaucoma, GI obstruction, megacolon, severe colitis, myasthenia gravis, obstructive uropathy, hypersensitivity to oxybutynin	Headache, pain, dry mouth, constipation, urinary retention, diarrhea, nausea, dyspepsia, dizziness

Landmark Neurology Trials

Trial	Reference	Results
NASCET	<i>NEJM</i> 1991; 7:445-53	Patients with symptomatic carotid stenosis of 70-99% benefited more from carotid endarterectomy than best medical therapy
NINDS t-PA	<i>NEJM</i> 1995; 333:1581-7	tPA reduces mortality and long-term disability when administered within 3 hours of acute stroke
ECASS 3	<i>NEJM</i> 2008; 359:1317-29	tPA improved clinical outcomes when administered within 3 to 4.5 hours of acute ischemic stroke
PROFESS	<i>NEJM</i> 2008; 359:1238-51	ASA + dipyridamole and clopidogrel showed similar benefits in secondary stroke prevention
SPARCL	<i>NEJM</i> 2006; 355:549-59	The observed benefit of statins in cardiovascular disease is also extended to patients with a recent stroke or TIA
Temporal lobe epilepsy + surgery	<i>NEJM</i> 2001; 345:311-8	Surgery is superior to prolonged medical therapy in temporal lobe epilepsy

References

Brain Death

Wijdicks EF. The Diagnosis of Brain Death. *NEJM* 2001; 344(16): 1215-21.

Coma

Bhidayasiri R, Waters MF, Giza CC (2005). Neurological differential diagnosis: a prioritized approach. Massachusetts: Blackwell Publishing, Inc., pp.71-2.
 Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, eds (2005). Harrison's principles of internal medicine, 16th edition. Toronto: McGraw-Hill Companies, Inc, pp. 1629-30.
 Common Presenting Complaints
 Bhidayasiri R, Waters MF, Giza CC (2005). Neurological differential diagnosis: a prioritized approach. Massachusetts: Blackwell Publishing, Inc, pp. 12-13, 305-14.

Headache

Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 2nd edition. Cephalalgia. 2004; 24(S1):9-160. <http://www.ihs-classification.org>.

Multiple Sclerosis

Ambati BK, Smith WT, Azer-Bentsianov MT (2001). Residents manual of medicine. Hamilton: BC Decker, pp. 211-13.
 Carpenter CCJ, Griggs RC, Loscalzo J, eds (2001). Cecil Essentials of medicine, 5th edition. Philadelphia: WB Saunders Co, pp. 973-6.
 Ferri FF (2001). Practical guide to the care of the medical patient. St. Louis: Mobsy Inc, pp. 654-656.
 Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *NEJM* 2000; 343(13): 938-52.
 Olek MJ, ed (2005). Multiple sclerosis: etiology, diagnosis, and new treatment strategies. New Jersey: Humana Press Inc, pp. 36-40, 57, 131, 222-23.
 Samuels MA, Feske SK, eds (2003). Office practice of neurology, 2nd edition. Philadelphia: Elsevier Science, pp. 410-11.
 Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos I, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005 Dec;58(6):840-6.
 Persistent Vegetative State
 Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, eds (2005). Harrison's principles of internal medicine, 16th edition. Toronto: McGraw-Hill Companies, Inc, pp. 1625.

Seizures and Epilepsy

Ambati BK, Smith WT, Azer-Bentsianov MT (2001). Residents manual of medicine. Hamilton: BC Decker, pp. 203-205.
 Ferri FF (2001). Practical guide to the care of the medical patient. St. Louis: Mobsy Inc, pp. 617-9.
 Carpenter CCJ, Griggs RC, Loscalzo J, eds (2001). Cecil Essentials of medicine, 5th edition. Philadelphia: WB Saunders Co, pp. 956-64.

Epilepsy

Griggs RC Cecil Essentials of Medicine 7th Edition Andreoli, Carpenter, Griggs, Benjamin. Saunders Elsevier pp 1120-8.

Status Epilepticus

Lowenstein DH, Alldredge BK. Status epilepticus. *NEJM* 1998;338(14):970-6.

Spinal Cord Syndrome

Wagner R, Jagoda A. Neurologic Emergencies: Spinal cord syndromes. *Emerg Med Clin North America* 1997; 15(3): 699-711.

Stroke

Lindsay K, Bone I., 2003 Neurology and Neurosurgery Illustrated. Philadelphia: Churchill Livingstone p. 244.
 Frontera W, Silver J. (2002) Essentials of Physical Medicine and Rehabilitation. Philadelphia: Hanley and Belfus Inc., p. 778-782.
 Organized Inpatient (stroke unit) care for stroke (Stroke Unit Trialists' Collaboration). The Cochrane Database of Systematic Reviews 2001; Issue 3.
 Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 2007;369:283-92.

Neuropathic Pain

Marcus, D. (2005). Chronic Pain – A Primary Guide to Practical Management. New Jersey: Humana Press. p. 111-28.

Wilson's Disease

Aminoff MJ, Greenberg DA, Simon RP. Lange: Clinical Neurology, 6th edition. Toronto: McGraw-Hill Companies, Inc. pp. 254-56.
 Disorders of the Motor System
 Marshall FJ. Cecil Essentials of Medicine 7th Edition Andreoli, Carpenter, Griggs, Benjamin. Saunders Elsevier pp 1090-100.

Dementia

Patterson C, Feightner JW, Garcia A, Hsiung GY, MacKnight C, Sadovnick AD. Diagnosis and treatment of dementia: 1. Risk assessment and primary prevention of Alzheimer disease. *CMAJ*. 2008 Feb 26;178(5):548-56.Review.
 Feldman HH, Jacova C, Robillard A, Garcia A, Chow T, Borrie M, et al. Diagnosis and treatment of dementia: 2. Diagnosis. *CMAJ*. 2008 March 25; 178(7):825-36. Review.

Predicting and Preventing Post-herpetic Neuralgia: Are current risk factors useful in clinical practice?

Coen PG, Scott F, Leedham-Green M et al. *European Journal of Pain* 2006;10:695-700.
 Chapter 24 Neurologic Disorders
 Yamada KA, Awadalla S. The Washington Manual of Medical Therapeutics, 31st Edition. Lippincott Williams and Wilkins pp 531-534.


Brian G. Ballios, Hubert Lee and Alireza Mansouri, chapter editors

Alaina Garbens and Modupe Oyewumi, associate editors

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 See Functional Neuroanatomy Software

Basic Anatomy Review

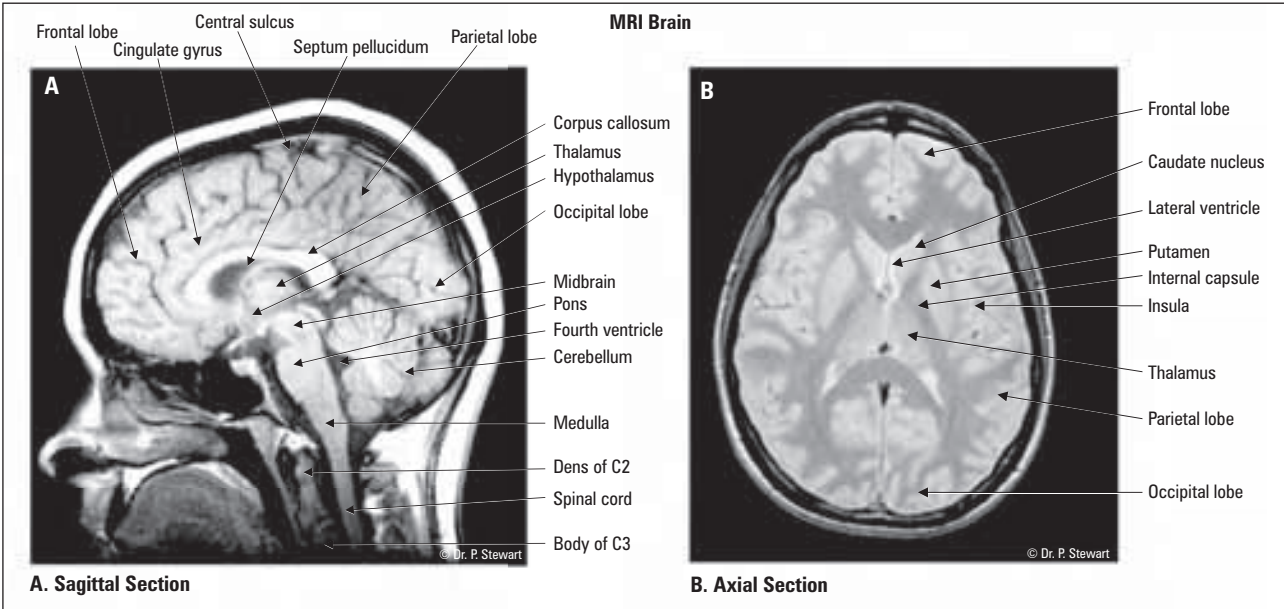


Figure 1. MRI Neuroanatomy
From Stewart P et al. *Functional Neuroanatomy* (Version 2.1). Health Education Assets Library, 2005.

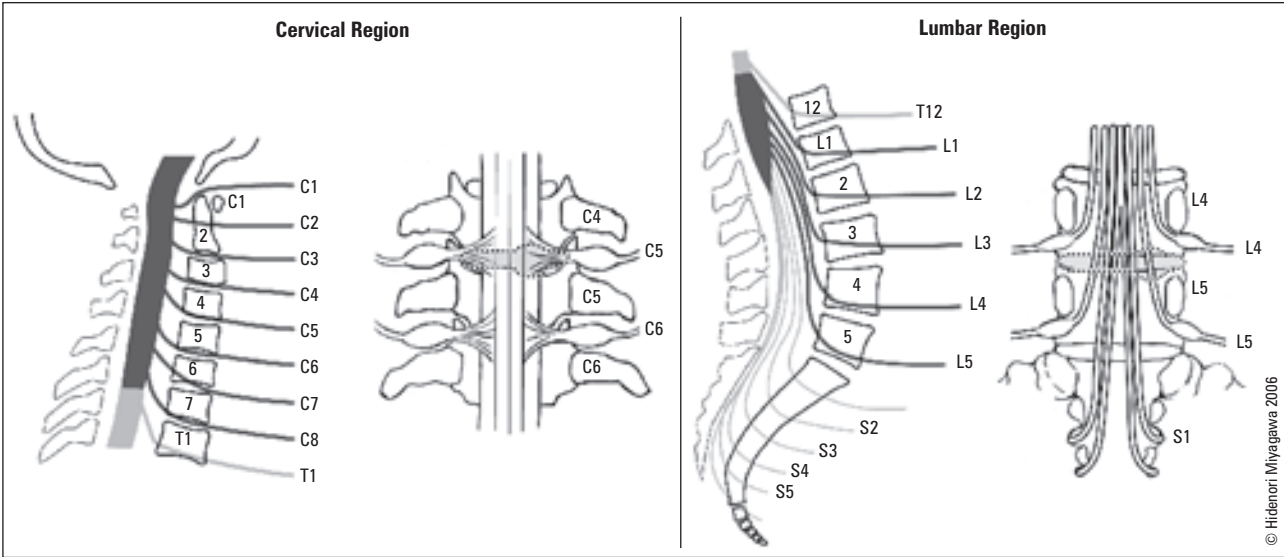


Figure 2. Relationship of Nerve Roots to Vertebral Level in the Cervical and Lumbar Spine
Note: AP views depict left-sided C4-5 and L4-5 disc herniation, and correlating nerve root impingement

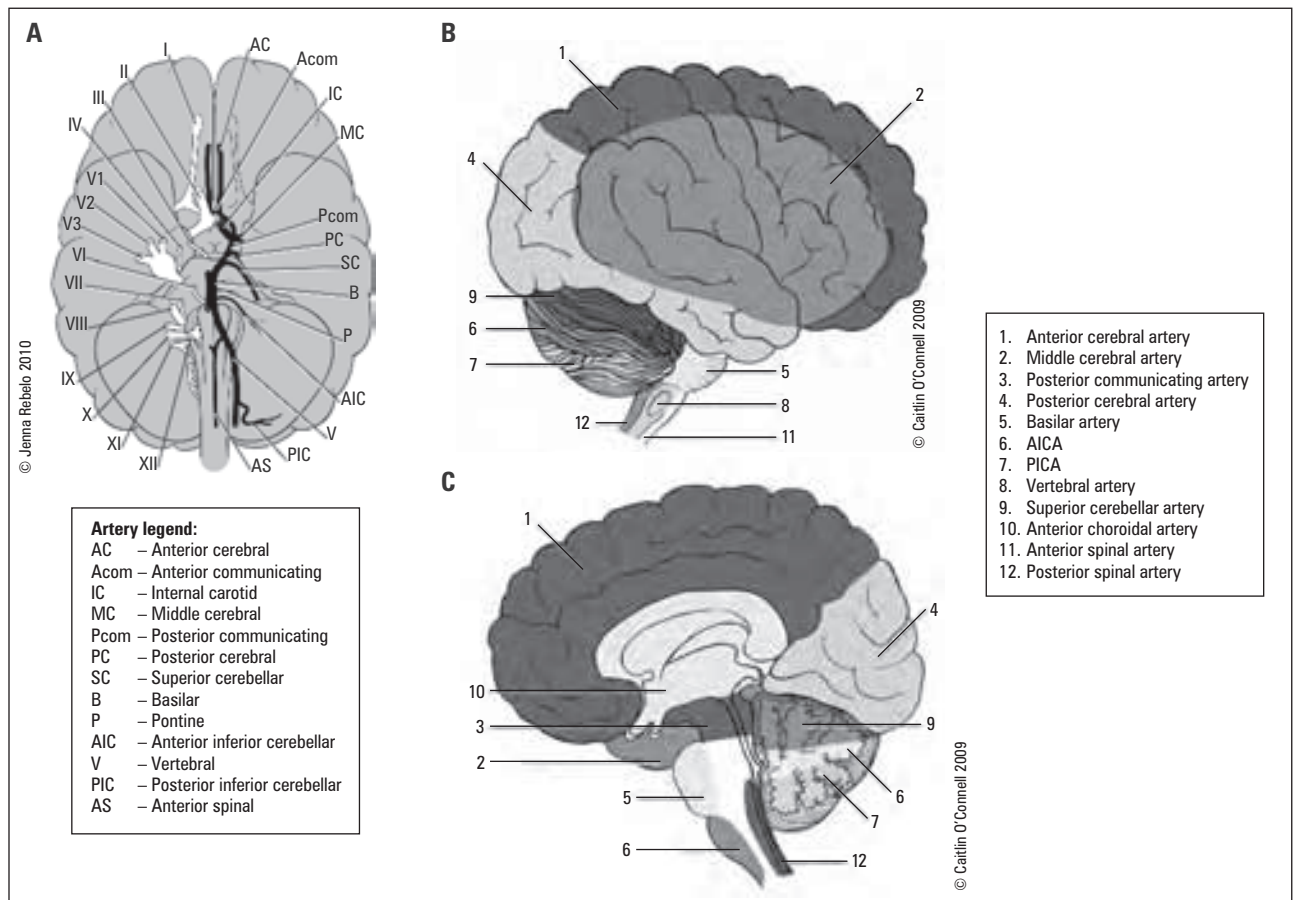


Figure 3. Vascular Supply of the Brain. Please refer to legend for artery names

Figure 3A. Circle of Willis, Most Common Variant

Figure 3B. Vascular Territories of the Brain and Brainstem, Sagittal View, Seen Laterally

Figure 3C. Vascular Territories of the Brain and Brainstem, Sagittal View, Seen Medially

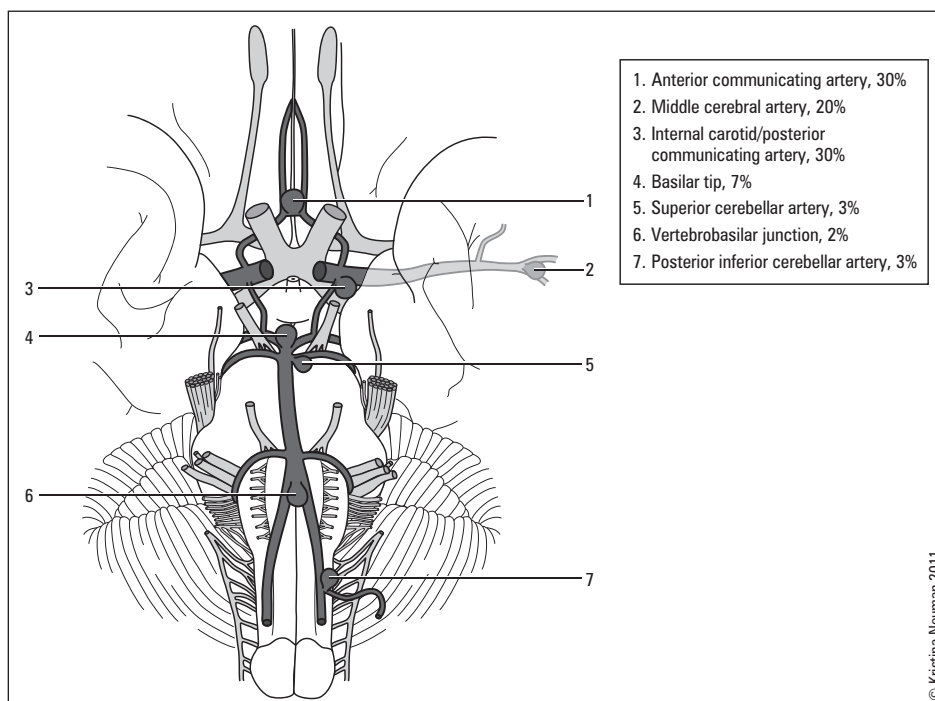


Figure 4. Aneurysms of the Circle of Willis

Differential Diagnoses of Common Neurosurgical Presentations

Intracranial Mass Lesions

- tumour
 - metastatic tumours
 - astrocytoma
 - meningioma
 - vestibular schwannoma (acoustic neuroma)
 - pituitary adenoma
 - primary CNS lymphoma
- pus/inflammation
 - cerebral abscess, extradural abscess, subdural empyema
 - encephalitis (see [Infectious Diseases](#), ID7)
 - tumefactive multiple sclerosis (MS)
- blood
 - extradural (epidural) hematoma
 - subdural hematoma
 - ischemic stroke
 - hemorrhage: subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH)
- cyst

Disorders of the Spine

- extradural
 - degenerative: disc herniation, canal stenosis, spondylolisthesis/spondylolysis
 - infection/inflammation: osteomyelitis, discitis
 - ligamentous: ossification of posterior longitudinal ligament (OPLL)
 - trauma: mechanical compression/instability, hematoma
 - tumours (55% of all spinal tumours): lymphoma, metastases (lymphoma, lung, breast, prostate), neurofibroma
- intradural extramedullary
 - vascular: dural arterio-venous fistula, subdural hematoma (especially if on anticoagulants)
 - tumours (40% of all spinal tumours): meningioma, schwannoma, neurofibroma
- intradural intramedullary
 - tumours (5% of all spinal tumours): astrocytomas and ependymomas most common; also hemangioblastomas and dermoid
 - syringomyelia (common causes: trauma, congenital, idiopathic)
 - infectious/inflammatory: TB, sarcoid, transverse myelitis
 - vascular: AVM, ischemia

Peripheral Nerve Lesions

- neuropathies
 - traumatic
 - entrapments
 - iatrogenic
 - inflammatory
 - tumours



Monro-Kellie Hypothesis

$$V_{\text{brain}} + V_{\text{blood}} + V_{\text{CSF}} + V_{\text{lesion}} = V_{\text{skull}} = \text{constant}$$

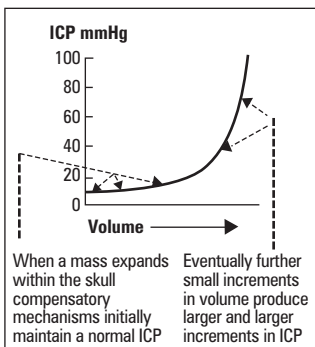


Figure 5. ICP-Volume Curve

Adapted from Lindsay KW, *Bone I: Neurology and Neurosurgery Illustrated*. Copyright 2004 with permission from Elsevier.

INTRACRANIAL PATHOLOGY

Intracranial Pressure (ICP) Dynamics

ICP/Volume Relationship

- adult skull is rigid with a constant intracranial volume
- contents (CSF, blood, brain) are incompressible
- increase in one constituent/space-occupying lesion = increase in ICP
- however, ICP does not rise initially due to compensatory mechanisms (autoregulation):
 - **immediate:** displacement of CSF to lumbar theca, blood
 - **delayed:** displacement of extracellular fluid (ECF) or intracellular fluid (ICF); displacement of brain tissue into compartments under less pressure (herniation)
- once compensation is exhausted, ICP rises exponentially

Cerebral Blood Flow (CBF)

- CBF depends on cerebral perfusion pressure (CPP) and cerebral vascular resistance (CVR)
- normal CPP >50 mmHg in adults
- cerebral autoregulation maintains constant CBF by compensating for changes in CPP, unless:
 - high ICP such that CPP <60 mmHg
 - MAP >150 mmHg or MAP <50 mmHg
 - brain injury: e.g. subarachnoid hemorrhage (SAH), severe trauma

ICP Measurement

Acute Monitoring

- lumbar puncture (LP) (see sidebar)
- intraventricular catheter/ventriculostomy/external ventricular drain ("gold standard", permits therapeutic drainage of CSF to decrease ICP)

Chronic Monitoring

- fibreoptic monitor (intraventricular, intraparenchymal, subdural), subarachnoid bolt (Richmond screw), and epidural monitor
- normal ICP <15 mmHg (8-18 cm H₂O) for adult, 3-7 mmHg (4-9.5 cm H₂O) for child; varies with patient position
 - moderate elevation: increase in mean pressure >20 mmHg
 - severe elevation: increase in mean pressure >40 mmHg
- waveform: comprised of respiratory and blood pressure pulsations (Traube-Hering waves); the amplitude increases with ICP
 - beta-waves: coarse, variably increased amplitude, frequency ½-2/min, often related to respiration
 - plateau waves: elevation of ICP over 50 mmHg lasting 5-20 min, precursor of further deterioration

Elevated ICP

Etiology

- intracranial space-occupying lesion:
 - tumour
 - pus
 - blood [trauma → hematoma (most common), subarachnoid hemorrhage]
 - depressed skull fracture
 - foreign body
- increased intracranial blood volume
 - vasodilatation (increased pCO₂/decreased pO₂/decreased extracellular pH, e.g. hypoventilation)
 - venous outflow obstruction (venous sinus thrombosis, superior vena cava syndrome, space occupying lesion)
 - cranial dependency
- cerebral edema
 - vasogenic (vessel damage, e.g. hypertensive encephalopathy, tumour)
 - cytotoxic (tissue/cell death, e.g. hypoxia, brain injury)
 - osmotic (acute hyponatremia, hepatic encephalopathy)
- impaired autoregulation (hypotension, hypertension, brain injury)
- hydrocephalus (obstructive, non-obstructive)
- tension pneumocephalus (gas within the cranial cavity)
- pseudotumour cerebri
- status epilepticus (chronic seizure resulting in brain edema)

Clinical Features

1. Acute Elevated ICP

- headache (H/A) – worse in the morning, aggravated by stooping and bending
- nausea and vomiting (N/V)
- decreased level of consciousness (LOC) if ICP = diastolic BP, or midbrain compressed
- drop in Glasgow Coma Scale (GCS) = best index to monitor progress and predict outcome of acute intracranial process (see *Neurotrauma*, NS29)
- papilledema ± retinal hemorrhages (may take 24-48 hours to develop)
- abnormal extra-ocular movements (EOM):
 - CN VI palsy: often falsely localizing (causative mass may be remote from nerve)
 - upward gaze palsy (especially in children with obstructive hydrocephalus)
- herniation syndromes (see *Herniation Syndromes*, NS6)
- focal signs/symptoms due to lesion



$$\text{CBF} = \text{CPP} / \text{CVR}$$

$$\text{CPP} = \text{MAP} - \text{ICP}$$

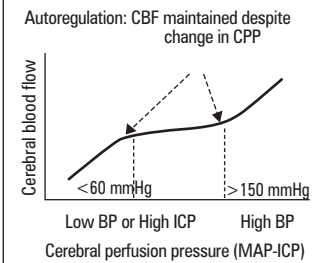


Figure 6. Cerebral Autoregulation Curve

Adapted from Lindsay et al. *Neurology and Neurosurgery Illustrated*. Copyright 2004 with permission from Elsevier.



Consider Monitoring of ICP in the following Situations

1. Patients with an abnormal head CT and Glasgow Coma Scale (GCS) score of 3 to 8 after cardiopulmonary resuscitation.
- Or
2. Patients with a normal head CT and GCS score of 3 to 8 AND the presence of two or more of the following:
 - Age over 40 years
 - Unilateral or bilateral motor posturing
 - Systolic blood pressure less than 90 mmHg
3. Postoperative monitoring
4. Investigation of normal pressure hydrocephalus (NPH)



Lumbar puncture is contraindicated with known/suspected intracranial mass.



Cushing's Triad of Acute Raised ICP (full triad seen in 1/3 of cases)

1. Hypertension
2. Bradycardia (late finding)
3. Abnormal respiratory pattern

2. Chronic Elevated ICP

- H/A
 - postural: worsened by coughing, straining, bending over
 - morning/evening H/A → vasodilatation due to increased CO₂ with recumbency
- visual changes
 - due to papilledema
 - enlarged blind spot, if advanced → episodic constrictions of visual fields (“grey-outs”)
 - optic atrophy/blindness
 - differentiate from papillitis (usually unilateral with decreased visual acuity)
- decreased level of consciousness

Investigations

- patients with suspected elevated ICP require an urgent CT/MRI
- ICP monitoring where appropriate

Herniation Syndromes

Table 1. Herniation Syndromes

Herniation Syndrome	Definition	Etiology	Clinical Features
1. Subfalcine	Cingulate gyrus herniates under falx	• Lateral supratentorial lesion	<ul style="list-style-type: none"> • Usually asymptomatic • Warnings of impending transtentorial herniation • Risk of ACA compression
2. Central Tentorial (Axial)	Displacement of diencephalon through tentorial notch	<ul style="list-style-type: none"> • Supratentorial midline lesion • Diffuse cerebral swelling • Late uncal herniation 	<ul style="list-style-type: none"> • Small pupils, moderately dilated, fixed (rostral to caudal deterioration), sequential failure of diencephalon, medulla • Decreased LOC (midbrain compression) EOM/upward gaze impairment (“sunset eyes”): compression of pretectum and superior colliculi • Brainstem hemorrhage (“Duret’s” – secondary to shearing of basilar artery perforating vessels) • Diabetes insipidus (traction on pituitary stalk and hypothalamus), end-stage sign
3. Lateral Tentorial (Uncal)	Uncus of temporal lobe herniates down through tentorial notch	• Lateral supratentorial lesion (often rapidly expanding traumatic hematoma)	<ul style="list-style-type: none"> • Ipsilateral non-reactive dilated pupil (earliest, most reliable sign) + ipsilateral EOM paralysis, ptosis (CN III compression) • Decreased LOC (midbrain compression) • Contralateral hemiplegia ± extensor (upgoing) plantar response ± ipsilateral hemiplegia (“Kernohan’s notch” – a false localizing sign resulting from pressure from the edge of the tentorium on the contralateral cerebral peduncle)
4. Upward	Cerebellar vermis herniates through tentorial incisura	• Large posterior fossa mass (common after VP shunting)	<ul style="list-style-type: none"> • Cerebellar infarct [superior cerebellar artery (SCA) compression] • Hydrocephalus (cerebral aqueduct compression)
5. Tonsillar	Cerebellar tonsils herniate through foramen magnum	<ul style="list-style-type: none"> • Infratentorial lesion • Following central tentorial herniation • Following LP in presence of intracranial mass lesion 	<ul style="list-style-type: none"> • Neck stiffness and head tilt (tonsillar impaction) • Decreased LOC (midbrain compression) • Flaccid paralysis • Respiratory irregularities, respiratory arrest (compression of medullary respiratory centres) • Blood pressure instability (compression of medullary cardiovascular centres)

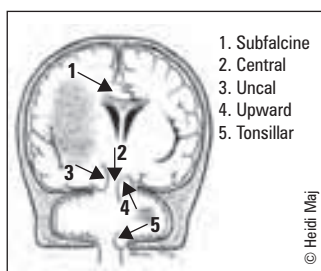


Figure 7. Herniation Types – See Table 1 for description

Treatment of Elevated ICP

- CT or MRI to identify etiology, assess for midline shift/herniation
- treat primary cause (i.e. remove mass lesions, ensure adequate ventilation)
- if elevated ICP persists following treatment of primary cause, consider therapy when ICP >20 mmHg
- goals: keep ICP <20 mmHg, CPP >65 mmHg, MAP >90 mmHg

General Measures (“ICP HEAD” see sidebar)

- elevate head of bed at 30-45°, maintain neck in neutral position → increases intracranial venous outflow
- prevent hypotension with fluid and vasopressors, dopamine, norepinephrine prn
- ventilate to normocarbica (pCO₂ 35-40 mmHg) → prevents vasodilatation
- oxygen prn to maintain pO₂ >60 mmHg → prevents hypoxic brain injury



Treatment of Elevated ICP:

ICP HEAD

Intubate
Calm (sedate)/Coma
Place drain/Paralysis

Hyperventilate
Elevate head
Adequate BP
Diuretic (mannitol)

Specific Measures

- osmolar diuresis (mannitol 20% IV solution 1-1.5 g/kg, then 0.25 g/kg q6h to serum osmolarity of 315-320)
 - can give rapidly, acts in 30 minutes, must maintain sBP >90 mmHg
- sedation ("light" e.g. barbiturates/codeine → "heavy" e.g. fentanyl/MgSO₄)
- paralysis with vecuronium → reduces sympathetic tone, reduces HTN induced by muscle contraction
- hyperventilate to pCO₂ 30-35 mmHg
 - use for brief periods only – also results in decreased cerebral blood flow (CBF)
- drain 3-5 ml CSF via ventricles, assess each situation independently
- insert external ventricular drain (if acute) or shunt
- corticosteroids → decrease edema over subsequent days around brain tumour, abscess, blood
 - no proven value in head injury or stroke
- hypothermia – cool body to 34°C
 - no proven value in head injury
- barbiturate coma induced with pentobarbital to reduce cerebral blood flow and metabolism (10 mg/kg over 30 min, then 1 mg/kg q1h continuous infusion)
 - decreases mortality, but no improvement in neurological outcome
- decompressive craniectomy is a last resort

Hydrocephalus

Definition

- increased CSF volume

Etiology

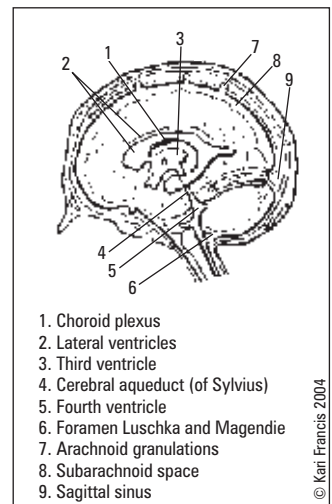
- obstruction to CSF flow
- decreased CSF absorption
- increased CSF production (rarely) – e.g. choroid plexus papilloma (0.4-1% of intracranial tumours)

Epidemiology

- estimated prevalence 1-1.5%; incidence of congenital hydrocephalus ~1-2/1000 live births
- hydrocephalus in children, see *Pediatric Neurosurgery*, NS37

Classification**Table 2. Classification of Hydrocephalus**

Disorder	Definition	Etiology	Findings on CT/MRI
Obstructive (Non-Communicating) Hydrocephalus	Circulation blocked within ventricular system proximal to the arachnoid granulations	Acquired <ul style="list-style-type: none"> Aqueductal stenosis (adhesions following infection, hemorrhage) Intraventricular lesions (tumours e.g. 3rd ventricle colloid cyst, hematoma) Mass causing tentorial herniation, aqueduct/4th ventricle compression Others: neurosarcoidosis, abscess/granulomas, arachnoid cysts Congenital <ul style="list-style-type: none"> Aqueductal stenosis, Dandy-Walker malformation, Chiari malformation (see <i>Pediatric Neurosurgery</i>, NS36) 	<ul style="list-style-type: none"> Ventricular enlargement proximal to block Periventricular hypodensity (transependymal migration of CSF forced into extracellular space) Sulcal effacement
Non-Obstructive (Communicating) Hydrocephalus	CSF absorption blocked at extraventricular site = arachnoid granulations	<ul style="list-style-type: none"> Post-infectious (#1 cause) → meningitis, cysticercosis Post-hemorrhagic (#2 cause) → SAH, IVH, traumatic Choroid plexus papilloma (rare, causes increased CSF production) Idiopathic → normal pressure hydrocephalus 	<ul style="list-style-type: none"> All ventricles dilated
Normal Pressure Hydrocephalus (NPH)	Persistent ventricular dilatation in the context of normal CSF pressure	<ul style="list-style-type: none"> Idiopathic (50%) Others: subarachnoid hemorrhage, meningitis, trauma, radiation-induced 	<ul style="list-style-type: none"> Enlarged ventricles without increased prominence of cerebral sulci
Hydrocephalus Ex Vacuo	Ventricular enlargement resulting from atrophy of surrounding brain tissue	<ul style="list-style-type: none"> Normal aging Alzheimer's, Creutzfeldt-Jacob Disease 	<ul style="list-style-type: none"> Enlarged ventricles and sulci Cerebral atrophy

**Figure 8. The Flow of CSF**

CSF produced by choroid plexus, flows to: ventricles → foramina of Luschka (lateral) and Magendie (medial) → subarachnoid space → absorbed by arachnoid villi/granulations into venous sinuses.

CSF production = CSF reabsorption = ~500 ml/day in normal adults
Normal CSF volume ~150 ml (50% spinal, 50% intracranial) → 25 ml intraventricular, 50 ml subarachnoid)

**NPH Progression**

AID
Ataxia/Apraxia of gait
Incontinence
Dementia

Clinical Features (see also *Pediatric Neurosurgery*, NS36)

- acute hydrocephalus
 - signs and symptoms of acute raised ICP (see *Elevated ICP*, NS5)
 - impaired upward gaze (“sunset eyes”) and/or CN VI palsy
- chronic/gradual onset hydrocephalus [i.e. normal pressure hydrocephalus (NPH)]
 - gradual onset of classic triad developing over weeks or months
 - ♦ pressure of ventricle on LE motor fibres → gait disturbance (ataxia and apraxia usually initial symptoms)
 - ♦ pressure on cortical bowel/bladder centre → urinary incontinence
 - ♦ pressure on frontal lobes → dementia
 - CSF pressure within clinically “normal” range, but symptoms abate with CSF shunting

Investigations

- CT/MRI
 - periventricular lucency suggests raised CSF pressure
- ultrasound (through anterior fontanelle in infants)
- ICP monitoring (e.g. LP) may be used to investigate NPH, test response to shunting (lumbar tap test)
- radionuclide cisternography can test CSF flow and absorption rate (unreliable)

Treatment

- ventricular drainage
- surgical removal of obstruction (if possible) or excision of choroid plexus papilloma
- shunts
 - ventriculoperitoneal (VP) – most common
 - ventriculopleural
 - ventriculo-atrial (VA) – not first choice because of increased infections, shunt emboli
 - lumboperitoneal – for communicating hydrocephalus and pseudotumour cerebri
- third ventriculostomy (for obstructive hydrocephalus) via ventriculocopy
- LPs [for transient hydrocephalus (e.g. subarachnoid hemorrhage), IVH in premature infants, etc.]

Shunt Complications**Table 3. Shunt Complications**

Complication	Etiology	Clinical Features	Investigations
Obstruction (most common)	<ul style="list-style-type: none"> • Obstruction by choroid plexus • Buildup of proteinaceous accretions, blood, cells (inflammatory or tumour) • Infection • Disconnection or damage 	<ul style="list-style-type: none"> • Acute hydrocephalus • Increased ICP 	<ul style="list-style-type: none"> • “Shunt series” (plain x-rays of entire shunt that only rule-out disconnection, break, tip migration) • CT • Radionuclide “shuntogram”
Infection (3-6%)	<ul style="list-style-type: none"> • <i>S. epidermidis</i> • <i>S. aureus</i> • <i>P. acnes</i> • Gram-negative bacilli 	<ul style="list-style-type: none"> • Fever, N/V, anorexia, irritability • Meningitis • Peritonitis • Signs and symptoms of shunt obstruction • Shunt nephritis (VA shunt) 	<ul style="list-style-type: none"> • CBC • Blood culture • Tap shunt for C&S (LP usually NOT recommended)
Overshunting (10% over 6.5 years)	<ul style="list-style-type: none"> • Slit ventricle syndrome • Collapse of ventricles leading to occlusion of shunt ports by ependymal lining • Secondary craniostylosis (children) 	<ul style="list-style-type: none"> • Chronic or recurring headaches often relieved when lying down • Slit-like ventricles on imaging 	<ul style="list-style-type: none"> • CT/MRI
	<ul style="list-style-type: none"> • Subdural hematoma • Collapsing brain tears bridging veins (especially common in NPH patients) 	<ul style="list-style-type: none"> • Asymptomatic • Headaches, vomiting, somnolence 	<ul style="list-style-type: none"> • CT
	<ul style="list-style-type: none"> • Apposition and overlapping of the cranial sutures in an infant following decompression of hydrocephalus 	<ul style="list-style-type: none"> • Abnormal head shape 	<ul style="list-style-type: none"> • Clinical • CT
Seizures (5.5% risk in 1st year, 1.1% after 3rd year)			<ul style="list-style-type: none"> • EEG
Inguinal Hernia (17% incidence with VP shunt inserted in infancy) ± skin breakdown over hardware	<ul style="list-style-type: none"> • Increased intraperitoneal pressure/fluid results in hernia becoming apparent 	<ul style="list-style-type: none"> • Inguinal swelling, discomfort 	<ul style="list-style-type: none"> • U/S

Benign Intracranial Hypertension (Pseudotumour Cerebri)

Definition

- raised intracranial pressure and papilledema without evidence of any mass lesion, hydrocephalus, infection or hypertensive encephalopathy (diagnosis of exclusion)

Etiology

- unknown (majority), but associated with:
 - lateral venous sinus thrombosis
 - habitus/diet: obesity, hyper/hypovitaminosis A
 - endocrine: reproductive age, menstrual irregularities, Addison's/Cushing's disease, thyroid irregularities
 - hematological: iron deficiency anemia, polycythemia vera
 - drugs: steroid administration or withdrawal, tetracycline, nalidixic acid, etc.
- risk factors overlap with those of venous sinus thrombosis; similar to those for gallstones ("fat, female, fertile, forties")

Epidemiology

- incidence ~0.5/100,000 per year
- usually in 3rd and 4th decade (F>M)

Clinical Features

- symptoms and signs of raised ICP (H/A in >90%, pulsatile intracranial noise), but NO decreased LOC or diplopia
- decreased visual acuity, papilledema, visual field defect, optic atrophy (key morbidity)
- usually self-limited, recurrence is common, chronic in some patients
- risk of blindness is not reliably correlated to symptoms or clinical course

Investigations

- CT: normal
- CSF studies: normal
- MRI: must look for venous sinus thrombosis

Treatment

- rule out conditions that cause intracranial hypertension
- discontinue offending medications, encourage weight loss, fluid/salt restriction
- pharmacotherapy: acetazolamide (decreases CSF production), thiazide diuretic or furosemide
- if above fail: serial LPs, shunt
- optic nerve sheath decompression (if progressive impairment of visual acuity)
- 2-year follow-up with imaging to rule out occult tumour, ophthalmology follow-up



Important features to note on CT and MRI (± contrast enhancement)

- Lesions (± edema, necrosis, hemorrhage)
- Midline shifts and herniations
- Effacement of ventricles and sulci (often ipsilateral), basal cisterns
- Single or multiple (multiple implies metastasis)



Primary CNS lymphoma reported in 6-20% of HIV infected patients.

Tumour

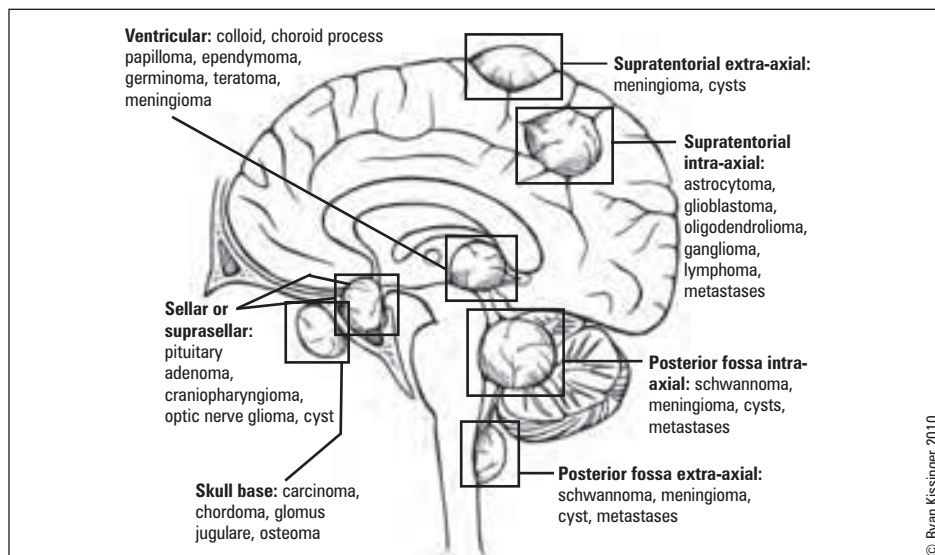


Figure 9. Tumours



DDx for Ring Enhancing Lesion on CT with Contrast

MAGICAL DR

- Metastases*
- Abscess*
- Glioblastoma (high grade astrocytoma)*
- Infarct
- Contusion
- AIDS (toxoplasmosis)
- Lymphoma
- Demyelination
- Resolving hematoma
- (* 3 most common Dx's)



Primary Sources of Metastatic Brain Tumours

Lung	44%
Breast	10%
Kidney (RCC)	7%
GI	6%
Melanoma	3%

Management of Single Brain Metastasis: A**Practice Guideline***Curr Oncol* 2007; 14(4):131-43

Patients identified as having single brain metastasis undergo treatment that include whole brain radiation therapy (WBRT), surgical resection and stereotactic radiation surgery (SRS). Given that conflicting evidence has been reported with respect to the best approach to single brain metastases, the Neuro-oncology Disease Site Group of the Cancer Care Ontario Program conducted a systematic review of the evidence and practice guideline.

Conclusions: Surgical excision should be considered for patients with good performance status, minimal or no evidence of extracranial disease, and a surgically accessible single brain metastasis amenable to complete excision. Because treatment in cases of single brain metastasis is considered palliative, invasive local treatments must be individualized. To reduce the risk of tumour recurrence for patients who have undergone resection of a single brain metastasis, postoperative WBRT should be considered. As an alternative to surgical resection, WBRT followed by SRS boost should be considered for patients with single brain metastasis. The evidence is insufficient to recommend SRS alone as a single-modality therapy.

Classification

- primary vs. metastatic, intra-axial (parenchymal) vs. extra-axial, supratentorial vs. infratentorial, adult vs. pediatric
- benign: non-invasive, but can be devastating due to expansion of mass in fixed volume of skull
- malignant: implies rapid growth, invasiveness, but rarely extracranial metastasis
- types of intracranial tumours (* = most common)
 - neuroepithelial
 - ♦ glial*: astrocytomas, oligodendrogliomas
 - ♦ neuronal: ganglion cell tumours, cerebral neurocytomas/neuroblastomas
 - ♦ poorly differentiated: glioblastomas, medulloblastomas
 - ♦ other: pineal tumours, ependymomas, choroid plexus papillomas
 - meningeal: meningiomas*
 - nerve sheath: schwannoma, neurofibroma
 - blood vessels: hemangioblastomas
 - germ cells: germinomas, teratomas
 - pituitary adenomas*
 - craniopharyngiomas
 - cysts: epidermoid/dermoid cysts, colloid cysts
 - local extension: chordomas, glomus jugulare tumours
 - other: primary CNS lymphomas, metastatic tumours

Clinical Features

- progressive neurological deficit (70%) – usually motor weakness, ± CN deficits, sensory, cognitive, personality, endocrine deficits (these may localize lesion)
- H/A (50%) ± raised ICP (acute or chronic depending on growth rate), H/A classically worse in am but non-specific (likely hypoventilation during sleep causing vasodilatation → increased ICP), may worsen with bending forward/valsava
- N/V (40%)
- seizures (25%)
- papilledema, vision changes
- symptoms suggestive of TIA (ictal, post-ictal, or ischemic 2° to “steal phenomenon”)
- rarely presents with hemorrhage
- familial syndromes associated with CNS tumours
 - von Hippel-Lindau (hemangioma)
 - tuberous sclerosis (astrocytoma)
 - neurofibromatosis type 1 and 2 (astrocytoma, acoustic neuroma respectively)
 - Li-Fraumeni (astrocytoma)
 - Turcot syndrome (glioblastoma multiforme)
 - multiple endocrine neoplasia type 1 (MEN-1) (pituitary adenoma)

Investigations

- CT, MRI, stereotactic biopsy (tissue diagnosis), metastatic work-up

Treatment

- conservative: serial Hx, Px, imaging for slow growing/benign lesions
- medical: corticosteroids to reduce cytotoxic cerebral edema, pharmacological (see *Pituitary Adenoma*, NS13)
- surgical: total or partial excision (decompressive, palliative), shunt if hydrocephalus
- radiotherapy: conventional fractionated radiotherapy (XRT), stereotactic radiosurgery (Gamma Knife®)
- chemotherapy: e.g. alkylating agents (temozolomide)

Table 4. Tumour Types: Age, Location

Age	Supratentorial	Infratentorial (posterior fossa)
< 15 years	Astrocytoma (all grades) (50%)	Medulloblastoma (15-20%)
• Incidence: 2-5/100,000/year	Craniopharyngioma (2-5%)	Cerebellar astrocytoma (15%)
• 60% infratentorial	Others: pineal region tumours, choroid plexus tumours, ganglioglioma, DNET	Ependymoma (9%)
		Brainstem astrocytoma
> 15 years	High grade astrocytoma (12-15%, e.g. GBM)	Metastasis
• 80% supratentorial	Metastasis (15-30%, includes infratentorial)	Acoustic neuroma (schwannoma) (5-10%)
	Meningioma (15-20%)	Hemangioblastoma (2%)
	Low grade astrocytoma (8%)	Meningioma
	Pituitary adenoma (5-8%)	
	Oligodendroglioma (5%)	
	Other: colloid cyst, CNS lymphoma, dermoid/epidermoid cysts	

Metastatic Tumours

- most common brain tumour seen clinically
- 15-30% of cancer patients present with cerebral metastatic tumours
 - most common sites = lungs, breast
 - other sites = kidney, thyroid, stomach, prostate, testis, melanoma
- haematogenous spread most common

Location

- 80% are hemispheric, often at grey-white matter junction or junction of temporal-parietal-occipital lobes (likely emboli spreading to terminal MCA branches)

Investigations

- identify primary tumour
 - metastatic work-up (CXR, CT chest/abdo, abdominal U/S, bone scan, mammogram)
 - CT with contrast → round, well-circumscribed, often ring enhancing, ++ edema, often multiple
 - MRI more sensitive, especially for posterior fossa
- consider biopsy in unusual cases, or if no primary identified
 1. metastatic work-up negative → brain biopsy
 2. metastatic work-up positive → biopsy of affected sites other than brain

Treatment

- medical
 - phenytoin for seizure prophylaxis if patient presents with seizure
 - dexamethasone to reduce edema given with ranitidine
 - chemotherapy (e.g. small cell lung cancer)
- radiation
 - stereotactic radiosurgery: for discrete, deep-seated/inoperable tumours
 - multiple lesions: use whole brain radiation therapy (WBRT); consider stereotactic radiosurgery if <3 lesions
 - post-op WBRT is commonly used
- surgical
 - single/solitary lesions: use surgery + radiation

Prognosis

- median survival without treatment once symptomatic is ~1 month, with optimal treatment 6-9 months but varies depending on primary tumour type

Astrocytoma

- most common primary intra-axial brain tumour

Table 5. Astrocytoma Grading System

World Health Organization (WHO)	Typical CT/MRI Findings	Survival
I – Pilocytic astrocytoma	± mass effect, ± enhancement	> 10 years, cure if gross total resection
II – Low grade/diffuse	Mass effect, no enhancement	5 years
III – Anaplastic	Complex enhancement	1.5-2 years
IV – Glioblastoma multiforme (GBM)	Necrosis (ring enhancement)	12 months, 10% at 2 years

Clinical Features

- epidemiology: most common in 4th-6th decades
- sites: cerebral hemispheres >> cerebellum, brainstem, spinal cord
- symptoms: recent onset of new/worsening H/A, N/V, seizure, ± focal deficits or symptoms of increased ICP

Investigations

- CT with contrast: variable appearance depending on grade (see Table 5)
- tissue biopsy: WHO grade and histology correlates with prognosis, but 25% chance of sampling error due to tumour heterogeneity

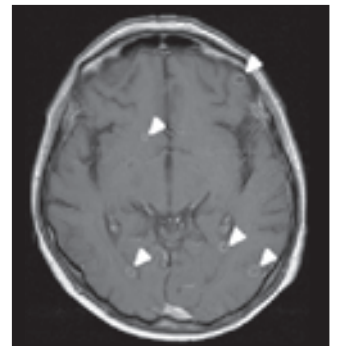


Figure 10. Multiple Brain Metastases (see arrows)

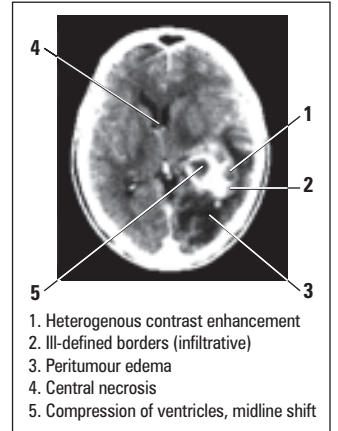


Figure 11. High Grade Astrocytoma on CT



Karnofsky General Cancer Performance Status Scale Rating Criteria

Rating Criteria (%)	
100	No complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of his personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Treatment

- low grade diffuse astrocytoma
 - close follow-up, radiation, chemotherapy, surgery all valid options
 - surgery: not curative, trend towards better outcomes
 - radiotherapy alone or post-op prolongs survival (retrospective evidence)
 - chemotherapy: usually reserved for tumour progression
- high grade astrocytomas (anaplastic astrocytoma and GBM)
 - surgery
 - ♦ gross total resection: maximal safe resection + fractionated radiation with 2 cm margin + concomitant and adjuvant temozolomide
 - except: extensive dominant lobe GBM, significant bilateral involvement, end of life near, extensive brainstem involvement
 - ♦ stereotactic biopsy if resection not possible, followed by fractionated radiation with 2 cm margin
 - expectant (based on functional impairment – Karnofsky score <70; patient's/family's wishes)
 - aim to prolong "quality" survival
 - chemotherapy: ~20% response rate, temozolomide (agent of choice); better response to temozolomide predicted by MGMT gene hypermethylation
- multiple gliomas: WBRT ± chemotherapy

Meningioma

- mostly benign (1-2% anaplastic), slow-growing, extra-axial, circumscribed (non-infiltrative), arise from arachnoid membrane
- often calcified, cause hyperostosis of adjacent bone
- classically see Psammoma bodies on histology

Common Locations

- parasagittal convexity or falx (70%), sphenoid wing, tuberculum sellae, foramen magnum, olfactory groove

Clinical Features

- middle aged, slight female preponderance (male:female = 2:3), high progesterone receptors (increase in size with pregnancy), symptoms of increased ICP, focal deficits, usually solitary (10% multiple, likely with loss of NF2 gene/22q12 deletion)

Investigations

- CT with contrast: homogeneous, densely enhancing, along dural border ("dural tail"), well circumscribed (Figure 12)
- contrast enhanced MRI provides better detail
- angiography
 - most are supplied by external carotid feeders (meningeal vessels)
 - also assesses venous sinus involvement, "tumour blush" commonly seen (prolonged contrast image)

Treatment

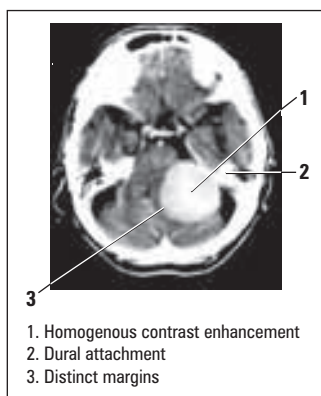
- conservative management for non-progressive, asymptomatic lesions
- surgery is treatment of choice if symptomatic or progression on sequential imaging (curative if complete resection)
- stereotactic radiosurgery (SRS) may be an option for lesions <3 cm
- endovascular embolization to facilitate surgery
- SRS or XRT for recurrent atypical/malignant meningiomas

Prognosis

- >90% 5-year survival, recurrence rate variable (often ~10-20%)
- depends on extent of resection (Simpson's classification)

Vestibular Schwannoma (Acoustic Neuroma)

- slow-growing (average of 1 mm/yr), benign posterior fossa tumour
- arises from vestibular component of CN VIII in internal auditory canal, expanding into bony canal and cerebello-pontine angle (CPA)
- if bilateral, diagnostic of neurofibromatosis type II
- epidemiology: all age groups affected, peaks at 4th-6th decades

**Figure 12. Meningioma on CT****WHO Classification of Meningioma (by histology)**

Grade 1: low risk of recurrence
Grade 2: intermediate risk of recurrence
Grade 3: high risk of recurrence



Progressive unilateral or asymmetrical sensorineural hearing loss = acoustic neuroma until proven otherwise.

Clinical Features

- compression of structures in CPA, often CN VIII (hearing loss 98%, tinnitus, dysequilibrium), then V, then VII
- ataxia and raised ICP are late features

Investigations

- MRI with gadolinium or T2 FIESTA sequence (>98% sensitive/specific), CT with contrast 2nd choice
- audiogram, brainstem auditory evoked potentials, caloric tests

Treatment

- conservative: serial imaging
- radiation: stereotactic radiosurgery is the treatment of choice
- surgery if: 1. lesion >3 cm; 2. brainstem compression; 3. edema; 4. hydrocephalus
 - curable if complete resection (almost always possible)
 - operative complications: CN VII, VIII dysfunction (only significant disability if bilateral), CSF leak

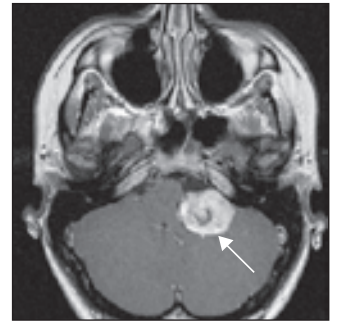


Figure 13. Vestibular Schwannoma
(tumour in cerebello-pontine angle)

Pituitary Adenoma

- primarily from anterior pituitary, 3rd-4th decades, M=F
- incidence in autopsy studies approximately 20%
- classification
 - microadenoma <1 cm; macroadenoma ≥1 cm
 - endocrine active (functional/secretory) vs. inactive (non-functional)

Clinical Features

- mass effects
 - H/A
 - bitemporal hemianopsia (compression of optic chiasm) (see Neurology, N21 for details of visual field deficit)
 - CN III, IV, V₁, V₂, VI palsy (compression of cavernous sinus)
- endocrine effects
 - hyperprolactinemia (prolactinoma): infertility, amenorrhea, galactorrhea, decreased libido
 - ACTH production: Cushing's disease, hyperpigmentation
 - GH production: acromegaly/gigantism
 - panhypopituitarism (hypothyroidism, hypoadrenalism, hypogonadism)
 - associated MEN-1 syndrome
 - diabetes insipidus
- pituitary apoplexy
 - apoplexy (sudden expansion of mass due to hemorrhage or necrosis)
 - abrupt onset H/A, visual disturbances, ophthalmoplegia, reduced mental status, and panhypopituitarism
 - CSF rhinorrhea and seizures (rare)
 - signs and symptoms of subarachnoid hemorrhage (rare)



Go Look For The Adenoma Please – GH, LH, FSH, TSH, ACTH, Prolactin
A compressive adenoma in the pituitary will impair hormone production in this order (i.e. GH-secreting cells are most sensitive to compression).

Investigations

- formal visual fields, CN testing
- endocrine tests (PRL level, TSH, 8 a.m. cortisol, fasting glucose, FSH/LH, IGF-1), electrolytes, urine electrolytes and osmolarity
- imaging (MRI with and without contrast)

Differential

- parasellar tumours (e.g. craniopharyngioma, tuberculum sellae meningioma), carotid aneurysm

Treatment

- medical
 - for apoplexy: rapid corticosteroid administration ± surgical decompression
 - for prolactinoma: dopamine agonists (e.g. bromocriptine)
 - for Cushing's: serotonin antagonist (cyproheptadine), inhibition of cortisol production (ketoconazole)
 - for acromegaly: somatostatin analogue (octreotide) ± bromocriptine
 - endocrine replacement therapy
- surgical
 - trans-sphenoidal, trans-ethmoidal, trans-cranial approaches



Pus

Sources of Pus/Infection

- four routes of microbial access to CNS
 1. hematogenous spread (most common): arterial and retrograde venous
 - ♦ adults: chest is #1 source (lung abscess, bronchiectasis, empyema)
 - ♦ children: congenital cyanotic heart disease with R to L shunt
 - ♦ immunosuppression (AIDS – toxoplasmosis)
 2. direct implantation: dural disruption due to
 - ♦ trauma
 - ♦ iatrogenic (e.g. following LP, post-op)
 - ♦ congenital defect (e.g. dermal sinus)
 3. contiguous spread (adjacent infection): from air sinus, naso/oropharynx, surgical site (e.g. otitis media, mastoiditis, sinusitis, osteomyelitis, dental abscess)
 4. spread from PNS (e.g. viruses: rabies, herpes zoster)
- common examples
 - epidural abscess: in cranial and spinal epidural space, associated with osteomyelitis
 - ♦ treatment: immediate drainage and antibiotics, surgical emergency if cord compression
 - subdural empyema: bacterial/fungal infection, due to contiguous spread from bone or air sinus, progresses rapidly
 - ♦ treatment: surgical drainage and antibiotics, 20% mortality
 - meningitis, encephalitis (see [Infectious Diseases](#), ID6)
 - cerebral abscess (see [Cerebral Abscess](#), below)

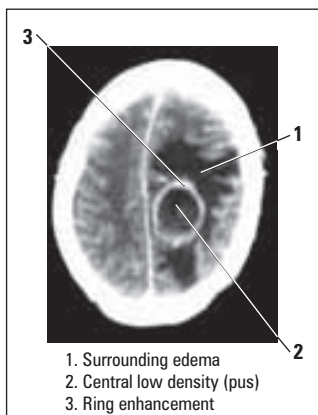


Figure 14. Brain Abscess on CT

Cerebral Abscess

Definition

- pus in brain substance, surrounded by tissue reaction (capsule formation)

Etiology

- modes of spread (see above): 10-60% of patients have no cause identified
- pathogens
 - *Streptococcus* (most common), often anaerobic or microaerophilic
 - *Staphylococcus* (penetrating injury)
 - Gram-negatives, anaerobes (*Bacteroides*, *Fusobacterium*)
 - in neonates: *Proteus* and *Citrobacter* (exclusively)
 - immunocompromised: fungi and protozoa: *Toxoplasma*, *Nocardia*, *Candida albicans*, *Listeria monocytogenes*, *Mycobacterium* and *Aspergillus*

Risk Factors

- lung abnormalities [infection, AV fistulas; especially Osler-Weber-Rendu syndrome (aka hereditary hemorrhagic telangiectasia)]
- congenital coronary heart disease: R-to-L shunt bypasses pulmonary filtration of micro-organisms
- bacterial endocarditis
- penetrating head trauma
- immunosuppression (e.g. AIDS)
- dental abscess

Clinical Features

- focal neurological signs and symptoms
 - H/A, decreased LOC; hemiparesis and seizures in 50%
- mass effect, increased ICP and sequelae (cranial enlargement in children)
- hemiparesis and seizures in 50%
- ± signs and symptoms of systemic infection (low-grade fever, leukocytosis)

Complications

- with abscess rupture: ventriculitis, meningitis, venous sinus thrombosis
- CSF obstruction
- transtentorial herniation

Investigations

- CT scan often 1st test in emergency department
- MRI
 - imaging of choice
 - apparent diffusion coefficient (ADC) used to differentiate abscess (black) from tumour (white)
- WBC/ESR may be normal, blood cultures rarely helpful and LP contraindicated if large mass
- CSF: nonspecific (high ICP, high WBC, high protein, normal carbohydrate), rarely helpful, usually negative culture

Brain abscess in 142 patients: factors influencing outcome and mortality

Surgical Neurology 2006; 65:557-562.

Introduction: This study looked to identify prognostic factors for outcome and mortality in patients with brain abscess.

Methods/Population: 165 patients from the National Taiwan University Hospital were reviewed retrospectively and included if (a) a localized brain parenchymal lesion with ring enhancement by contrast was visible on CT or MRI and (b) was associated with at least 1 of positive blood cultures, positive cultures of intracerebral materials or histology of the intracerebral lesion suggesting brain abscess. 142 (98 male, mean age 41.5 years, range 2-84) patients satisfied these criteria. Demographical and clinical data was collected and outcome was assessed according to the Glasgow Outcome Score (GOS). All patients were treated with IV antibiotics for at least 4 weeks. Drainage and excision was performed on lesions >2.5 cm in largest diameter.

Results: A total of 105 patients had favourable outcome: 63 (44.4%) had full recovery and 42 (29.6%) had mild deficits. 37 patients had an unfavourable outcome, 24 died in hospital and 13 had moderate to severe disability. Multivariate logistic regression showed improved outcome associated with being male (OR 9.81, $P=0.002$), having a presenting GCS >12 (OR 6.20, $P=0.019$), being sepsis-free throughout hospitalization (OR 761.49, $P<0.001$) or having gram-positive cocci grown from abscess culture (OR 42.3, $P=0.013$). No other variables proved to be prognostic.

Conclusion: Surgical management (craniotomy drainage, stereotactic aspiration or excision) is recommended in all patients with regards to obtaining culture materials, even when the abscess is small (<2.5 cm), deeply seated or multiple in nature. The improved prognosis associated with being sepsis-free and/or growing gram-positive cocci, likely results in part from having culture and sensitivity analysis to guide appropriate antimicrobial management.

Treatment

- aspiration ± excision and send for Gram stain, acid fast bacillus (AFB), C&S, fungal culture
- excision preferable if location suitable
- antibiotics
 - empirically: vancomycin + ceftriaxone + metronidazole or chloramphenicol or rifampin (6-8 weeks therapy)
 - revise antibiotics when C&S known
- anti-convulsants (1-2 years)
- follow up CT is critical (do weekly initially, more frequent if condition deteriorates)

Prognosis

- mortality with appropriate therapy ~10%, permanent deficits in ~50%

Blood

Table 6. Comparison of Epidemiology and Etiology of Intracranial Bleeds

Types of Hematoma/Hemorrhage	Etiology	Epidemiology	Clinical Features	CT Features	Treatment	Prognosis
Epidural Hematoma	Skull fracture causing middle meningeal bleed	Male > Female (4:1)	Lucid interval before LOC	Lenticular mass	Craniotomy	Good with prompt management (Note: respiratory arrest can occur from uncal herniation)
Acute Subdural Hematoma	Ruptured subarachnoid bridging vessels	Age >50, associated with trauma	No lucid interval, hemiparesis, Pupillary changes	Crescentic mass	Craniotomy if bleed >1 cm	Poor
Chronic Subdural Hematoma	Ruptured subarachnoid bridging vessels	Age >50, EtOH abusers, anti-coagulated	Often asymptomatic Minor H/A, confusion, signs of increased ICP	Hypodense crescentic mass	Burr hole to drain; craniotomy if reoccurs	Good
Subarachnoid Hemorrhage	Trauma, spontaneous (aneurysms, idiopathic, AVM)	Age 55-60 20% cases under age 45	Sudden onset thunderclap headache, signs of increased ICP	High density blood (sensitivity decreases over time)	Conservative: NPO, IV NS, ECG, Foley, BP 120-150, vasospasm prophylaxis (nimodipine); open vs. endovascular surgery to repair if rebleed	Poor: 50% mortality 30% of survivors have moderate to severe disability
Intracerebral Hemorrhage	HTN, vascular abnormality, tumours, infections, coagulopathy	Age >55, male, drug use (cocaine, EtOH, amphetamine)	TIA-like symptoms, signs of increased ICP	High density blood	Medical: decrease BP, control ICP Surgical: Craniotomy	Poor: 44% mortality due to cerebral herniation

Extradural ("Epidural") Hematoma

Etiology

- temporal-parietal skull fracture: 85% are due to ruptured middle meningeal artery. Remainder of cases are due to bleeding from middle meningeal vein, dural sinus, or bone/diploic veins

Epidemiology

- young adult, male > female = 4:1; rare before age of 2 or after age 60

Clinical Features

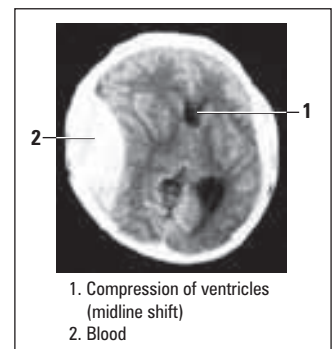
- in 60%, there is lucid interval of several hours between concussion and coma
- then, obtundation, hemiparesis, ipsilateral pupillary dilatation
- signs and symptoms depend on severity but can include H/A, N/V, amnesia, altered LOC, HTN and respiratory distress
- deterioration can take hours to days

Investigations

- CT without contrast: high density biconvex mass against skull, "lenticular-shaped," usually with uniform density and sharp margins, usually limited by suture lines

Treatment

- admit, observe, head elevation
- mannitol pre-op if elevated ICP/brain herniation
- craniotomy to evacuate clot, follow up CT

**Figure 15. Extradural Hematoma on CT**

Calcium antagonists for aneurysmal subarachnoid haemorrhage (Review)

Cochrane Review 2008; Issue 3.

Introduction: This study looked to review the evidence in regards as to whether calcium antagonists improve the outcome in patients with aneurysmal subarachnoid haemorrhage.

Methods/Population: The review included 3361 patients presenting with aneurysmal subarachnoid haemorrhage from 16 randomised controlled trials comparing treatment with calcium antagonists vs. control from 1980 to March 2006.

Results: The results were based mainly on one large trial of oral nimodipine, which showed a RR of 0.67 (95% CI 0.55 to 0.81) and the evidence for other calcium agonists was not statistically significant.

Conclusion: The authors endorse the use of oral nimodipine in patients with aneurysmal subarachnoid haemorrhage.



CT Density and MRI Appearance of Blood

Time	CT	MRI -T1	MRI -T2
Acute (<72h)	Hyper.	Grey	Black
Subacute (<4w)	Iso.	White	White
Chronic (>4w)	Hypo.	Black	Black

MRI-T1: "George Washington Bridge"
MRI-T2: "Oreo" cookie –
Black/White/Black

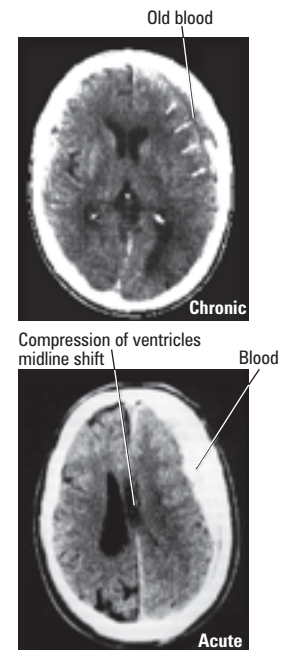


Figure 16. Subdural Hematoma on CT

Prognosis

- good with prompt management, as the brain is often not damaged
- worse prognosis if bilateral Babinski or decerebration pre-op
- death is usually due to respiratory arrest from uncus herniation (injury to the midbrain)

Subdural Hematoma



ACUTE SUBDURAL HEMATOMA

Etiology

- rupture of vessels that bridge the subarachnoid space (e.g. cortical artery, large vein, venous sinus) or cerebral laceration

Risk Factors

- trauma, anticoagulants, alcohol, cerebral atrophy, infant head trauma (see [Pediatrics](#))

Clinical Features

- no lucid period, signs and symptoms can include altered LOC, pupillary irregularity, hemiparesis

Investigations

- CT: high density concave mass, "crescentic" usually less uniform, less dense and more diffuse than extradural hematoma

Treatment

- craniotomy for clinically symptomatic subdural hemorrhage, or subdurals greater than 1 cm; optimal if surgery <4 hrs from onset

Prognosis

- poor overall since the brain is often injured (mortality range is over 50%)

CHRONIC SUBDURAL HEMATOMA

Etiology

- many start out as acute subdurals
- blood within the subdural space evokes an inflammatory response:
 - fibroblasts invasion of clot and formation of neomembranes within days → neocapillaries growth → fibrinolysis and liquefaction of blood clot
- course is determined by the balance of rebleeding from neomembranes and resorption of fluid

Risk Factors

- older, alcoholics, patients with CSF shunts, anticoagulants, coagulopathies

Clinical Features

- often due to minor injuries or no history of injury
- may present with minor H/A, confusion, language difficulties, TIA-like symptoms, symptoms of raised ICP ± seizures, progressive dementia, gait problem
- obtundation disproportionate to focal deficit; "the great imitator" of dementia, tumours

Investigations

- CT: hypodense (liquefied clot), crescentic mass

Treatment

- seizure prophylaxis only if posttraumatic seizure
- reverse coagulopathies
- burr hole drainage as clot liquefies; craniotomy if recurs more than twice

Prognosis

- good overall as brain usually undamaged, but may require repeat drainage

Cerebrovascular Disease



Ischemic Cerebral Infarction (80%)

- embolic (heart, carotid artery, aorta) or thrombosis of intracerebral arteries (see *Carotid Stenosis*, NS21 and *Neurology*, N45)

Intracranial Hemorrhage (20%)

- subarachnoid hemorrhage (SAH), spontaneous intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH)

Subarachnoid Hemorrhage (SAH)



Definition

- bleeding into subarachnoid space (intracranial vessel between arachnoid and pia)

Etiology

- trauma (most common)
- spontaneous
 - aneurysms (75-80%)
 - idiopathic (14-22%)
 - AVMs (5%)
- coagulopathies (iatrogenic or primary), vasculitides, tumours (<5%)

Epidemiology

- ~10-28/100,000 population/year
- peak age 55-60, 20% of cases occur under age 45

Risk Factors

- hypertension
- pregnancy/parturition in patients with pre-existing AVMs, eclampsia
- oral contraceptive pill
- substance abuse (cigarette smoking, cocaine, alcohol)
- conditions associated with high incidence of aneurysms (see *Intracranial Aneurysms*, NS20)

Clinical Features of Spontaneous SAH

- sudden onset (seconds) of severe "thunderclap" headache usually following exertion and described as the "worst headache of my life" (up to 97% sensitive, 12-25% specific)
- nausea/vomiting, photophobia
- meningismus (neck pain/stiffness, positive Kernig's and Brudzinski's sign)
- decreased LOC (due to either raised ICP, ischemia, seizure)
- focal deficits: cranial nerve palsies (CN III, IV), hemiparesis
- ocular hemorrhage in 20-40% (due to sudden raised ICP compressing central retinal vein)
- reactive hypertension
- sentinel bleeds
 - SAH-like symptoms lasting <1 day ("thunderclap H/A")
 - may have blood on CT or LP
 - ~50% of patients with full blown SAH give history suggestive of sentinel bleed within past 3 weeks
- differential diagnosis: sentinel bleed, dissection/thrombosis of aneurysm, venous sinus thrombosis, benign exertional H/A

Investigations

- non-contrast CT (Figure 17)
 - 98% sensitive within 12h, 93% within 24h; 100% specificity
 - may be negative if small bleed or presentation delayed several days
 - acute hydrocephalus, IVH, ICH, infarct or large aneurysm may be visible
- CTA/MRA/cerebral angiography for localization and treatment planning
- positive history for SAH with negative CT – MUST do LP to look for blood or xanthochromia (may be negative <12h)
- lumbar puncture (LP) findings (highly sensitive):
 - elevated opening pressure (>18 cm H₂O)
 - bloody initially, xanthochromic supernatant with centrifugation ("yellow") by ~12h, lasts 2 weeks
 - RBC count usually >100,000/mm³ without significant drop from 1st to last tube (in contrast to traumatic tap)
 - elevated protein due to blood breakdown products



Fisher Grade (SAH on CT scan)

Grade	Finding
1	Normal scan
2	<1 mm thick blood
3	>1 mm thick blood
4	IVH or ICH ± SAH



Hunt and Hess Grade (clinical grading scale for SAH)

Grade	Description
1	No Sx or mild H/A and/or mild meningismus
2	Features of 1 + CN palsy
3	Confusion/lethargy, mild hemiparesis or aphasia
4	GCS <15 but >8, moderate-severe hemiparesis, mild rigidity
5	Coma (GCS <9), decerebrate, moribund appearance

Mortality of Grade 1-2 20%, increased with grade



World Federation of Neurological Surgeons Grading of SAH

WFNS Grade	GCS Score	Aphasia, Hemiparesis, or Hemiplegia
0 *		
1	15	—
2	13-14	—
3	13-14	+
4	7-12	+ or —
5	3-6	+ or —

*Intact aneurysm

- four vessel cerebral angiography (“gold standard” for aneurysms)
 - demonstrates source of SAH in 80-85% of cases
 - “angiogram negative SAH”: repeat angiogram in 7-14 days, if negative → “perimesencephalic SAH”
- magnetic resonance angiography (MRA) and CT angiography
 - sensitivity may be up to 95% for aneurysms

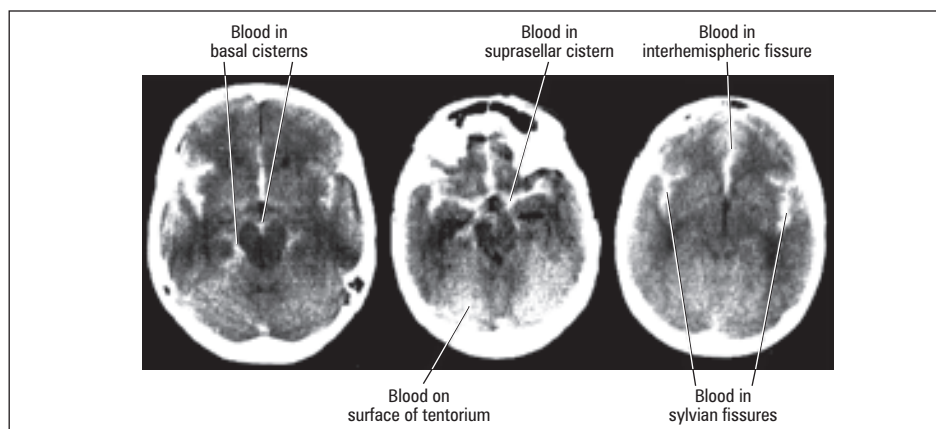


Figure 17. Diagnosis of SAH

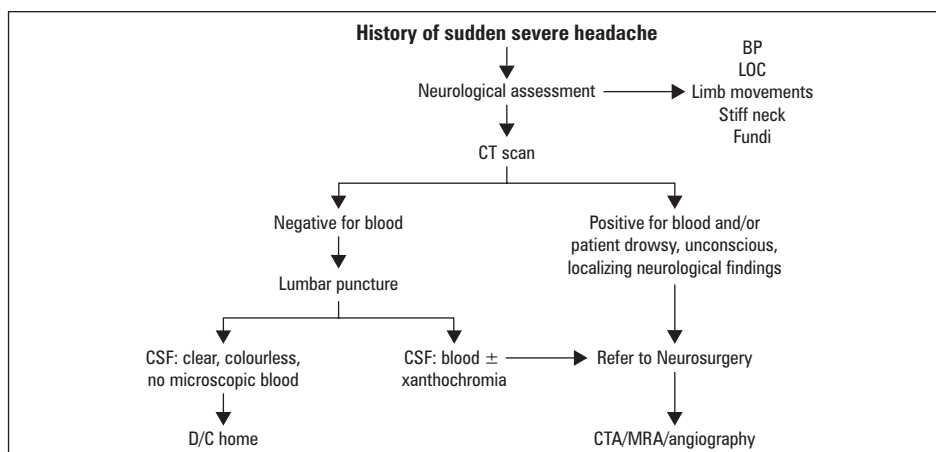


Figure 18. Approach to SAH

Treatment

- admit to ICU or NICU
- oxygen/ventilation prn
- NPO, bed rest, elevate head of bed 30°, minimal external stimulation, neurological vitals q1h
- aim to maintain sBP = 120-150 (balance of vasospasm prophylaxis, risk of re-bleed, risk of hypotension since CBF autoregulation impaired by SAH)
- cardiac rhythm monitor
- Foley prn, strict monitoring of ins and outs
- IV NS with 20 mmol KCl/L at 125-150 cc/h
- phenytoin if seizure or temporal lobe clot
- mild sedation prn
- nimodipine for vasospasm neuroprotection for 21 days; may discontinue earlier if patient is clinically well

Complications

- vasospasm – vessel constriction in response to extravascular blood irritation
 - clinical features: confusion, decreased LOC, focal deficit (speech or motor)
 - onset: 4-14 days post-SAH (deterioration within first 3 days is NOT caused by vasospasm)
 - risk factors: large amount of blood on CT (high Fisher grade), smoking, increased age, HTN
 - “symptomatic” vasospasm in 20-30% of SAH patients
 - “radiographic” vasospasm in 30-70% of arteriograms performed 7 days following SAH (peak incidence)
 - diagnosed clinically, and/or with transcranial Doppler (increased velocity of blood flow)
 - risk of cerebral infarct and death
 - treatment
 - ♦ “triple H” therapy using fluids and pressors (examples: norepinephrine, phenylephrine)
 - ♦ angioplasty for refractory cases
- hydrocephalus (15-20%) – due to blood obstructing CSF drainage
 - can be acute or chronic, requires extraventricular drain (EVD) or shunt, respectively
- neurogenic pulmonary edema
- hyponatremia – SIADH, cerebral salt wasting
- diabetes insipidus
- cardiac – arrhythmia (>50% have ECG changes), MI, CHF



“Triple H” Therapy for Vasospasm
 Hypertension
 Hypervolemia
 Hemodilution

Prognosis

- 10-15% mortality before reaching hospital, overall 50% mortality (majority within first 2-3 weeks)
- 30% of survivors have moderate to severe disability
- a major cause of mortality is rebleeding, for aneurysms:
 - risk of rebleed: 4% on first day, 15-20% within 2 weeks, 50% by 6 months
 - if no rebleed by 6 months, risk decreases to same incidence as unruptured aneurysm (2%)
 - only prevention is early clipping or coiling of “cold” aneurysm
 - rebleed risk for “perimesencephalic SAH” is approximately same as for general population

Intracerebral Hemorrhage (ICH)



Definition

- hemorrhage within brain parenchyma, accounts for ~10% of strokes
- can dissect into ventricular system (IVH) or through cortical surface (SAH)

Etiology

- hypertension (usually causes bleeds at putamen, thalamus, pons and cerebellum)
- hemorrhagic transformation (reperfusion post stroke, surgery, strenuous exercise, etc.)
- vascular anomalies
 - aneurysm, AVMs and other vascular malformations (see *Vascular Malformations*, NS22)
 - venous sinus thrombosis
 - arteriopathies (cerebral amyloid angiopathy, lipohyalinosis, vasculitis)
- tumours (1%) – often malignant (e.g. GBM, lymphoma, metastases)
- drugs (amphetamines, cocaine, alcohol, anticoagulants, etc.)
- coagulopathy (iatrogenic, leukemia, TTP, aplastic anemia)
- CNS infections (fungal, granulomas, herpes simplex encephalitis)
- post trauma (immediate or delayed, frontal and temporal lobes most commonly injured via coup/contre-coup mechanism)
- eclampsia
- post-operative (post-carotid endarterectomy cerebral reperfusion, craniotomy)
- idiopathic

Epidemiology

- 12-15 cases/100,000 population/year

Risk Factors

- increasing age (mainly >55 years)
- male gender
- hypertension
- Black/Asian > Caucasian
- previous CVA of any type (23x risk)
- both acute and chronic heavy alcohol use; cocaine, amphetamines
- liver disease
- anticoagulants

Clinical Features

- TIA-like symptoms often precede ICH, can localize to site of impending hemorrhage
- location: basal ganglia/internal capsule (50%), thalamus (15%), cerebral white matter (15%), cerebellum/brainstem – usually pons (15%)
- gradual onset of symptoms over minutes-hours, usually during activity
- H/A, N/V and decreased LOC are common
- specific symptoms/deficits depend on location of ICH

Investigations

- hyperdense blood on noncontrast CT

Treatment

- medical
 - decrease BP to pre-morbid level or by ~20%; check PTT/INR, and correct coagulopathy (stop anticoagulation for 1-2 weeks)
 - control raised ICP (see *Intracranial Pressure Dynamics* section, NS4)
 - phenytoin for seizure prophylaxis
 - follow electrolytes (SIADH common)
 - angiogram to r/o vascular lesion unless >45 yrs, known HTN, and putamen/thalamic/posterior fossa ICH (yield ~ 0%)
- surgical
 - craniotomy with evacuation of clot, treatment of source of ICH (i.e. AVM, tumour, cavernoma), ventriculostomy to treat hydrocephalus
 - indications
 - ♦ symptoms of raised ICP or mass effect
 - ♦ rapid deterioration (especially if signs of brainstem compression)
 - ♦ favourable location, e.g. cerebellar, non-dominant hemisphere
 - ♦ young patient (<50 yrs)
 - ♦ if tumour, AVM, aneurysm, or cavernoma suspected (resection or clip to decrease risk of rebleed)
 - contraindications
 - ♦ small bleed: minimal symptoms, GCS >10
 - ♦ poor prognosis: massive hemorrhage (especially dominant lobe), low GCS/coma, lost brainstem function
 - ♦ medical reasons [e.g. very elderly, severe coagulopathy, difficult location (e.g. basal ganglia, thalamus)]

Prognosis

- 30-day mortality rate 44%, mostly due to cerebral herniation
- rebleed rate 2-6%, higher if HTN poorly controlled



Intracranial Aneurysms

Epidemiology

- prevalence 1-4% (20% have multiple)
- female > male; age 35-65 years

Risk Factors

- autosomal dominant polycystic kidney disease (15%)
- fibromuscular dysplasia (7-21%)
- AVMs
- connective tissue diseases (Ehlers-Danlos, Marfan's)
- family history
- bacterial endocarditis
- Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia)
- atherosclerosis and HTN
- trauma

Types (Figure 4, NS3)

- saccular (berry)
 - most common type
 - located at branch points of major cerebral arteries (Circle of Willis)
 - 85-95% in carotid system, 5-15% in vertebrobasilar circulation
- fusiform
 - atherosclerotic
 - more common in vertebrobasilar system, rarely rupture
- mycotic
 - secondary to any infection of vessel wall, 20% multiple
 - 60% *Streptococcus* and *Staphylococcus*
 - 3-15% of patients with SBE

Table 7. 5-year Cumulative Rupture Risk in Unruptured Aneurysms Based on Size and Location

	Cavernous Carotid	AC/MC/IC	Vertebrobasilar/PC/PComm
<7 mm	0%	0%	2.5%
7-12 mm	0%	2.6%	14.5%
13-24 mm	3%	14.5%	18.4%
≥24 mm	6.4%	40%	50%

AC – anterior cerebral/anterior communicating artery; MC – middle cerebral artery; IC – internal carotid artery; PC – posterior cerebral artery; PComm – posterior communicating artery
The Lancet 2003;362:103-10

Clinical Presentation

- rupture (90%), most often SAH, but 30% ICH, 20% IVH, 3% subdural bleed
- sentinel hemorrhage (“thunderclap H/A”) → requires urgent clipping/coiling to prevent catastrophic bleed
- mass effect (giant aneurysms)
 - internal carotid or anterior communicating aneurysm may compress:
 - ♦ the pituitary stalk or hypothalamus causing hypopituitarism
 - ♦ the optic nerve or chiasm producing a visual field defect
 - basilar artery aneurysm may compress midbrain, pons (limb weakness), or CN III
 - posterior communicating artery aneurysm may produce CN III palsy
 - intracavernous aneurysms (CN III, IV, V₁, V₂, VI)
- distal embolization (e.g. amaurosis fugax)
- seizures
- headache (without hemorrhage)
- incidental CT or angiography finding (asymptomatic)

Investigations

- CT angiogram (CTA), magnetic resonance angiography (MRA), angiogram

Treatment

- ruptured aneurysms
 - overall trend towards better outcome with early surgery or coiling (48-96 hours after SAH)
 - treatment options: surgical placement of clip across aneurysm neck, trapping (clipping of proximal and distal vessels), thrombosing using Guglielmi detachable coils (coiling), wrapping (last resort)
 - choice of surgery vs. coiling not yet well defined, consider location, size, shape, and tortuosity of the aneurysm, patient comorbidities, age, and neurological condition. In general:
 - ♦ coiling: posterior > anterior circulation, deep/eloquent location, basilar artery bifurcation/apex, older age, presence of comorbidities, presence of vasospasm
 - ♦ clipping: superficial > deep, broad aneurysmal base, branching arteries at the aneurysm base, tortuosity/atherosclerosis of afferent vessels, dissection, hematoma, acute brainstem compression
- unruptured aneurysms
 - average 1% annual risk of rupture: risk dependent on size and location of aneurysm
 - no clear evidence on when to operate: need to weigh life expectancy
 - risk of morbidity/mortality of SAH (20%/50%) vs. surgical risk (2%/5%)
 - generally treat unruptured aneurysms >10 mm
 - consider treating when aneurysm 7-9 mm in middle-aged, younger patients or patients with a family history of aneurysms
 - follow smaller aneurysms with serial angiography

International Subarachnoid Aneurysm Trial (ISAT) of Neurosurgical Clipping versus Endovascular Coiling in 2143 Patients with Ruptured Intracranial Aneurysms: A Randomised Comparison of Effects on Survival, Dependency, Seizures, Rebleeding, Subgroups, and Aneurysm Occlusion

Lancet 2005; 366:809-17

This randomized trial aimed to compare endovascular detachable coiled treatment against craniotomy and clipping for ruptured intracranial aneurysms in patients who were considered eligible for either modality of therapy.

Conclusion: In patients with ruptured intracranial aneurysms suitable for both treatments, endovascular coiling is more likely to result in independent survival at 1 year than neurosurgical clipping; the survival benefit continues for at least 7 years. The risk of late rebleeding is low, but is more common after endovascular coiling than after neurosurgical clipping.

Carotid Stenosis



Definition

- narrowing of the internal carotid artery lumen due to atherosclerotic plaque formation, usually near common carotid bifurcation into internal and external carotids

Risk Factors

- for atherosclerosis: HTN, smoking, DM, CVD or CAD, dyslipidemia

Clinical Features

- may be asymptomatic
- symptomatic stenosis may present as TIA, reversible ischemic neurologic deficit (RIND), or stroke
- retinal insufficiency or infarct permanently or temporarily (amaurosis fugax), (see [Neurology](#), N47 and [Ophthalmology](#), OP37)
- middle cerebral artery (MCA) occlusive symptoms

Prevention of Disabling and Fatal Strokes by Successful Carotid Endarterectomy in Patients Without Recent Neurological Symptoms: Randomised Controlled Trial

Lancet 2004; 363:1491-1502

Study: Asymptomatic Carotid Surgery Trial (ACST), a randomized, controlled trial with follow-up at 5 years.

Patients: 3120 asymptomatic patients with significant carotid artery stenosis were randomized equally between immediate carotid endarterectomy (CEA) and indefinite deferral of CEA and were followed for up to 5 years (mean 3.4 years).

Main Outcome: Any stroke (including fatal or disabling).

Conclusions: In asymptomatic patients with significant carotid artery stenosis, immediate CEA reduced the net 5-year stroke risk from about 12% to about 6%. Half of this 5-year benefit involved disabling or fatal strokes.

Investigations

- CBC, PTT/INR (hypercoagulable states)
- fundoscopy: cholesterol emboli in retinal vessels (Hollenhorst plaques)
- auscultation over carotid bifurcation for bruits
- carotid duplex Doppler ultrasound: determines size of lumen and blood flow velocity, safest but least accurate, unable to scan above mandible
- angiogram: "gold standard" but invasive and 1/200 risk of stroke (not for screening)
- MRA: safer than angiogram, may overestimate stenosis

Treatment

- control of HTN, lipids, diabetes
- antiplatelet agents (ASA ± dipyridamole, clopidogrel) ~25% relative risk reduction
- carotid endarterectomy (generally if symptomatic and >70% stenosis, see Tables 8 and 9)
- endovascular angioplasty ± stenting

Prognosis

Table 8. Symptomatic Carotid Stenosis: North American Symptomatic Carotid Endarterectomy Trial (NASCET)

% Stenosis on Angiogram	Risk of Major Stroke or Death	
	Medical Rx	Medical + Surgical Rx
70-99 %	26% over 2 years	9% over 2 years
50-69%	22% over 5 years	16% over 5 years
<50%	Surgery has no benefit with 5% complication rate	

Table 9. Asymptomatic Carotid Stenosis: Asymptomatic Carotid Atherosclerosis Study (ACAS) and Asymptomatic Carotid Surgery Trial (ACST)

% Stenosis on Angiogram	Risk of Major Stroke or Death	
	Medical Rx	Medical + Surgical Rx
60-99%	11% over 5 years	5.1% over 5 years (ACAS)
70-99%	11.8% over 5 years	6.4% over 5 years (ACST)



Vascular Malformations

Types

- arteriovenous malformations (AVMs)
- cavernous malformations (cavernoma, cavernous hemangioma/angioma)
- venous angioma
- capillary telangiectasias
- arterio-venous fistula (AVF) (carotid-cavernous fistula, dural AVF, vein of Galen aneurysm)
- "angiographically occult vascular malformations" (any type, 10% of malformations)
- clinical significance:
 - AVMs and cavernous malformations produce intracranial hemorrhages and seizures

Arteriovenous Malformations (AVMs)

Definition

- tangle of abnormal vessels/arteriovenous shunts, with no intervening capillary beds or brain parenchyma
- congenital

Epidemiology

- prevalence ~0.14%, male:female = 2:1, average age at diagnosis = 33 years
- 15-20% of patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) will have cerebral AVMs

Clinical Features

- hemorrhage (40-60%) – small AVMs are more likely to bleed due to direct high pressure AV connections
- seizures (50%) – more common with larger AVMs
- mass effect
- focal neurological signs secondary to ischemia (high flow → "steal phenomena")
- localized headache, increased ICP
- bruit (especially with dural AVMs)
- may be asymptomatic ("silent")



Spetzler-Martin AVM Grading Scale

Item	Score
Size	
0-3 cm	1
3.1-6.0 cm	2
> 6 cm	3
Location	
Noneloquent	0
Eloquent	1
Deep venous drainage	
Not present	0
Present	1

AVM grades calculated by adding the 3 individual Spetzler-Martin Scale scores from the above table. E.g. A 2 cm tumour in noneloquent location without deep venous drainage = Grade I.

Investigations

- MRI (flow void), MRA
- angiography (7% will also have one or more associated aneurysms)

Treatment

- decreases risk of future hemorrhage and seizure
 - surgical excision is treatment of choice
 - stereotactic radiosurgery (SRS) is preferred for small (<3 cm) or very deep lesions
 - endovascular embolization (glue, balloon) can facilitate surgery or SRS for larger lesions
- conservative (e.g. palliative embolization, seizure control if necessary)

Prognosis

- 10% mortality, 30-50% morbidity (serious neurological deficit) per bleed
- risk of major bleed in untreated AVMs: 2-4% per year

Cavernous Malformations

Definition

- benign vascular hamartoma consisting of irregular sinusoidal vascular channels located within the brain without intervening neural tissue or associated large arteries/veins

Epidemiology

- 0.1-0.2%, both sporadic and hereditary forms described
- several genes now described: CCM1, CCM2, CCM3

Clinical Features

- seizures (60%), progressive neurological deficit (50%), hemorrhage (20%), H/A
- often an incidental finding
- hemorrhage risk less than AVM, usually minor bleeds

Investigations

- T2WI MRI (non-enhancing); gradient echo sequencing (best for diagnosis)
- usually not seen with angiography or CT

Treatment

- surgical excision
 - only appropriate for symptomatic lesions that are surgically accessible (supratentorial lesions are less likely to bleed than infratentorial lesions)

Prognosis

- good with surgical intervention

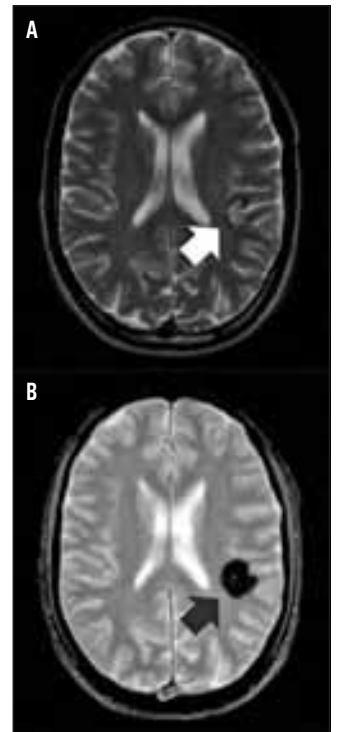


Figure 19. MRI of Cavernous Malformation

A. T2 weighted imaging MRI

B. Gradient Echo sequencing MRI



Important Dermatomes and Myotomes

C2 – Angle of jaw
 C4 – Collar of shirt
 "C3,4,5 keeps the diaphragm alive"
 T4 – Nipple line
 T6 – Xiphoid
 T10 – Umbilical
 T12 – Suprapubic
 "L3 above the knee"
 "S2,3,4 – Keeps your stool off the floor"



Myotomes

C5 – Shoulder abduction/elbow flexion
 C6 – Wrist extensors
 C7 – Elbow extension
 C8 – Squeeze hand
 T1 – Abduct fingers
 T2-9 – Intercostal (Abdominal reflexes)
 T9-10 – Upper abdominals
 T11-12 – Lower abdominals
 L2 – Flex hip
 L3 – Hip adduction
 L4 – Knee extension and ankle dorsiflexion
 L5 – Ankle dorsiflexion and big toe extension
 S1 – Plantarflex foot



Reflexes

1, 2 tie my shoe → S1-2 Ankle jerk
 3, 4 kick the door → L3-4 Knee
 5, 6 pick up sticks → C5-6 Biceps/Brachioradialis
 7, 8 lay them straight → C7-8 Triceps



RED FLAGS for Back Pain

Cauda Equina

Urinary retention or incontinence, fecal incontinence or loss of anal sphincter tone, saddle anesthesia, uni/bilateral, leg weakness/pain.

Malignancy

Age > 50, previous hx of cancer, pain unrelieved by bed rest, constitutional symptoms.

Infection.

Increased ESR, IV drug use, immunosuppressed, fever.

Compression Fracture

Age > 50, trauma, prolonged steroid use.



RED FLAGS for Back Pain

BACK PAIN

Bowel/Bladder (retention or incontinence)

Anesthesia (saddle)

Constitutional symptoms

Chronic disease

Parasthesia

Age > 50 or < 20

IV drug use

Neuromotor deficits

EXTRACRANIAL PATHOLOGY

Dermatomes/Myotomes

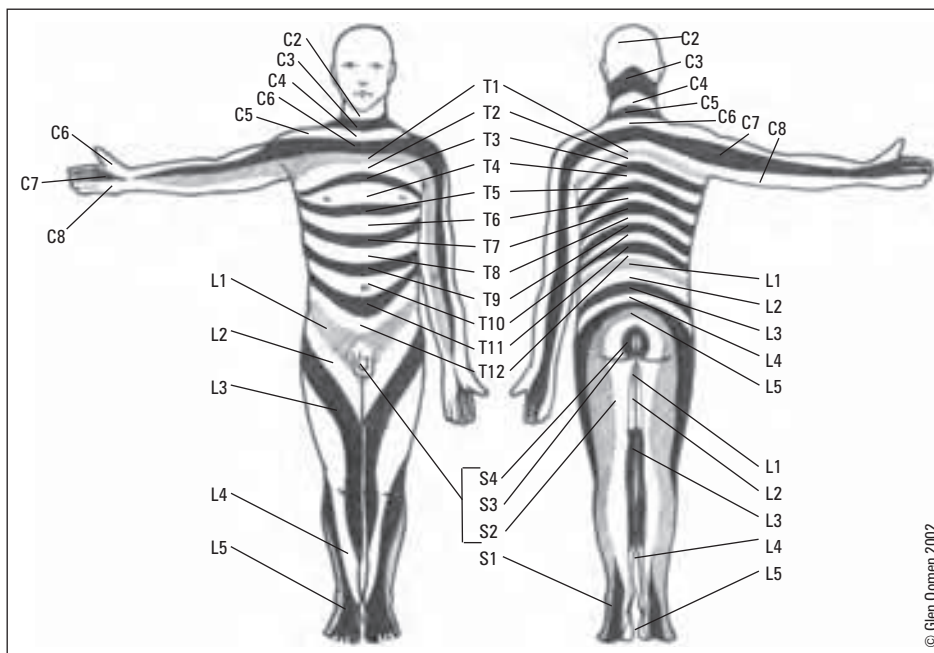


Figure 20. Dermatomes

Approach to Limb/Back Pain

- see Orthopaedics, OR22

Extradural Lesions

Root Compression

Differential Diagnosis

- herniated disk
- neoplasm (neurofibroma, schwannoma)
- synovial cyst, abscess
- hypertrophic bone/spur

Cervical Disc Syndrome

Etiology

- nucleus pulposus herniates through annulus fibrosis and impinges upon nerve root

Epidemiology

- most common levels C6-C7 (C7 root) > C5-C6 (C6 root)

Clinical Features

- pain down arm in nerve root distribution, worse with neck extension, ipsilateral rotation and lateral flexion (all compress the ipsilateral neural foramen)
- LMN signs and symptoms
- central cervical disc protrusion causes myelopathy as well as nerve root deficits

Investigations

- if red flags: C-spine x-ray, CT, MRI (imaging of choice)
- consider EMG, nerve conduction studies if diagnosis uncertain

Treatment

- conservative
 - no bedrest unless severe radicular symptoms
 - activity modification, patient education (reduce sitting, lifting)
 - physiotherapy, exercise programs
 - analgesics, collar, traction may help
- surgical indications
 - intractable pain despite adequate conservative treatment for >3 months
 - progressive neurological deficit
 - anterior cervical discectomy is usual surgical choice

Prognosis

- 95% improve spontaneously in 4-8 weeks

Table 10. Lateral Cervical Disc Syndromes

	C4-5	C5-6	C6-7	C7-T1
Root Involved	C5	C6	C7	C8
Incidence	2%	19%	69%	10%
Sensory	Shoulder	Thumb	Middle finger	Ring finger, 5th finger
Motor	Deltoid, biceps, supraspinatus	Biceps	Triceps	Digital flexors, intrinsic
Reflex	No change	Biceps, Brachioradialis	Triceps	Finger jerk (Hoffmann's sign)

Cervical Stenosis (Cervical Spondylosis)

Definition

- cervical spondylosis is chronic disc degeneration and associated facet arthropathy
- resultant syndromes include mechanical neck pain, radiculopathy (root compression), myelopathy (spinal cord compression) and combinations

Epidemiology

- typically begins at age 40-50, men > women, most commonly at the C5-C6 > C6-C7 levels

Pathogenesis

- with neck extension, the cervical cord is pinched. With neck flexion, the canal dimensions increase slightly to relieve pressure on the cervical cord

Clinical Features

- insidious onset of mechanical neck pain exacerbated by excess vertebral motion (particularly rotation and lateral bending with a vertical compressive force – Spurling's test). Pain is worse with neck extension, relieved with flexion
- occipital headache is common
- radiculopathy may involve 1 or more roots, and symptoms include neck, shoulder and arm pain, paresthesias and numbness
- cervical myelopathy may be characterized by weakness (upper > lower extremity), decreased dexterity and sensory changes. UMN findings such as hyperreflexia, clonus and Babinski reflex may be present. The most worrisome complaint is lower extremity weakness (corticospinal tracts)
- myelopathy may be associated with funicular pain, characterized by burning and stinging ± Lhermitte's sign (lightning-like sensation down the back with neck flexion)

Investigations

- x-ray of cervical spine ± flexion/extension or oblique views (studied for changes in Luschka and facet joints, osteophytes and disc space narrowing), MRI, CT, EMG

Treatment

- NSAIDs, moist heat, strengthening and range of motion exercises, analgesics, cervical collar, cervical traction
- surgical indications: myelopathy with motor impairment, progressive neurologic impairment, intractable pain



Disc herniations impinge the nerve root at the level below the interspace (i.e. C5-6 disc affects the C6 nerve root).



Sensory Fibres

Fasciculus gracilis/cuneatus: joint position, fine touch, vibration
Spinothalamic tract: Pain and temperature

Motor Fibres

Corticospinal tract: skilled movements

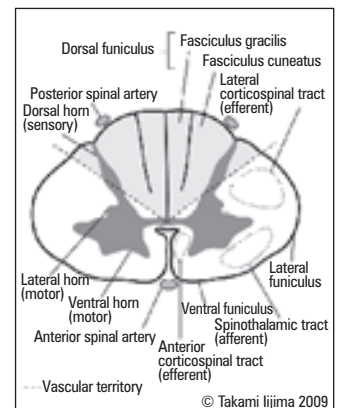


Figure 21A. Axial section of Cervical Spine with Vascular and Functional Territories

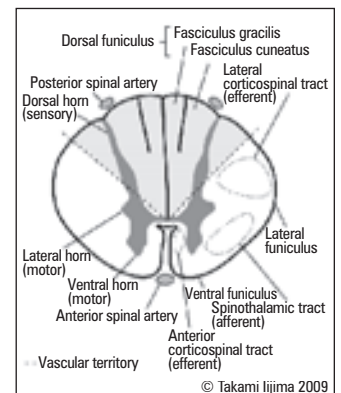


Figure 21B. Axial section of Thoracic Spine with Vascular and Functional Territories

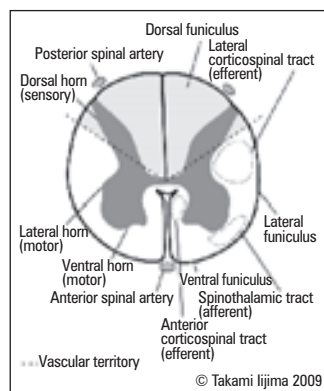


Figure 21C. Axial section of Lumbar Spine with Vascular and Functional Territories

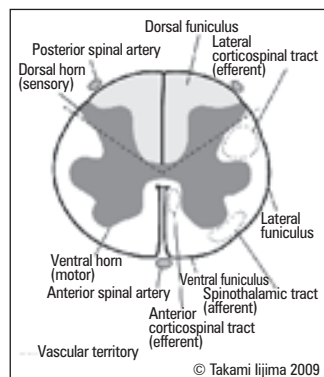


Figure 21D. Axial section of Sacral Spine with Vascular and Functional Territories

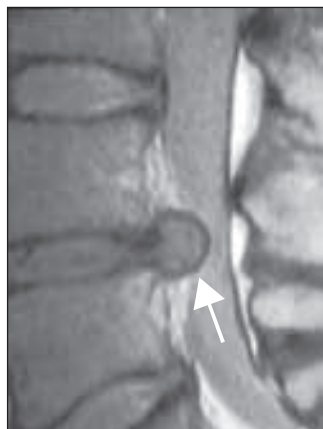


Figure 22. T2-weighted MRI of Lumbar Disc Herniation

Lumbar Disc Syndrome

Etiology

- laterally herniated lumbar disc compresses nerve root, central herniation causes cauda equina or lumbar stenosis (neurogenic claudication)

Epidemiology

- common (>95% of herniated lumbar disks) – L5 and S1 roots

Clinical Features

- leg pain > back pain
- limited back movement (especially forward flexion) due to pain
- motor weakness, dermatomal sensory changes, reflex changes
- exacerbation with coughing, sneezing or straining. Relief with flexing the knee or thigh
- nerve root tension signs
 - straight leg raise (SLR: Lasegue's test) or crossed SLR (pain should occur at less than 60 degrees) suggests L5, S1 root involvement
 - femoral stretch test suggests L2, L3 or L4 root involvement

Investigations

- x-ray spine (only to rule out other lesions), CT, MRI
- myelogram and post-myelogram CT (only if MRI is contraindicated)

Treatment

- conservative (same as cervical disc disease)
- surgical indications
 - same as cervical disc + cauda equina syndrome

Prognosis

- 95% improve spontaneously within 4 to 8 weeks

Table 11. Lateral Lumbar Disc Syndromes

	L3-4	L4-5	L5-S1
Root Involved	L4	L5	S1
Incidence	<10%	45%	45%
Pain	Femoral pattern	Sciatic pattern	Sciatic pattern
Sensory	Medial leg	Dorsal foot to hallux Lateral leg	Lateral foot
Motor	Tibialis anterior (dorsiflexion)	Extensor hallucis longus (hallux extension)	Gastrocnemius, soleus (plantar flexion)
Reflex	Knee jerk	Medial hamstrings	Ankle jerk

Table 12. Differentiating Conus Medullaris Syndrome from Cauda Equina Syndrome

	Conus Medullaris Syndrome	Cauda Equina Syndrome
Onset	Sudden, bilateral	Gradual, unilateral
Spontaneous Pain	Rare, if present usually bilateral, symmetric in perineum or thighs	Severe, radicular type: in perineum, thighs, legs, back, or bladder
Sensory Deficit	Saddle; bilateral and symmetric; sensory dissociation	Saddle; no sensory dissociation; may be unilateral and asymmetric
Motor Deficit	Symmetric; paresis less marked; fasciculations may be present	Asymmetric; paresis more marked; atrophy may be present; fasciculations rare
Reflexes	Only ankle jerk absent (preserved knee jerk)	Knee and ankle jerk may be absent
Autonomic Symptoms (bladder dysfunction, impotence, etc.)	Urinary retention and atonic anal sphincter prominent early; impotence frequent	Sphincter dysfunction presents late; impotence less frequent

Cauda Equina Syndrome



Etiology

- compression or irritation of lumbosacral nerve roots below conus medullaris (below L2 level)
- decreased space in the vertebral canal below L2
- common causes: herniated disk \pm spinal stenosis, vertebral fracture and tumour

Clinical Features

- usually acute (develops in less than 24 hours); rarely subacute or chronic
- motor (LMN signs)
 - weakness/paraparesis in multiple root distribution
 - reduced deep tendon reflexes (knee or ankle)
- autonomic
 - urinary retention (or overflow incontinence) and/or fecal incontinence due to loss of anal sphincter tone
- sensory
 - low back pain radiating to legs (sciatica) aggravated by Valsalva maneuver and by sitting; relieved by lying down
 - bilateral sensory loss or pain: depends on the level affected
 - saddle area (S2-S5) anesthesia
 - sexual dysfunction (late finding)



Spinal cord ends at L1-2; dura ends at S1-2.

Treatment

- urgent investigation and decompression (<48 hrs) to preserve bowel, bladder and sexual function and/or to prevent progression to paraplegia

Prognosis

- markedly improves with surgical decompression
- recovery correlates with function at initial presentation: if patient is ambulatory, likely to continue to be ambulatory; if unable to walk, unlikely to walk after surgery

Lumbar Spinal Stenosis

Etiology

- congenital narrowing of spinal canal combined with degenerative changes (herniated disk, hypertrophied facet joints and ligamentum flavum)

Clinical Features

- gradually progressive back and leg pain with standing and walking that is relieved by sitting or lying down (neurogenic claudication – 60% sensitive)
- neurologic exam may be normal, including straight leg raise test

Investigations

- spine x-ray, CT, MRI, myelogram

Treatment

- conservative – NSAIDs, analgesia
- surgical – laminectomy with root decompression

Neurogenic Claudication

Etiology

- ischemia of lumbosacral nerve roots secondary to vascular compromise and increased demand from exertion, often associated with lumbar stenosis

Clinical Features

- dermatomal pain/paresthesia/weakness of buttock, hip, thigh, or leg initiated by standing or walking
- slow relief with postural changes (sitting >30 min), NOT simply exertion cessation
- induced by variable degrees of exercise or standing
- may be elicited with lumbar extension, but may not have any other neurological findings, no signs of vascular compromise (e.g. ulcers, poor capillary refill, etc.)

Investigations

- bicycle test may help distinguish neurogenic claudication (NC) from vascular claudication (the waist-flexed individuals on the bicycle with NC can last longer)

Treatment

- same as for lumbar spinal stenosis



Key Features of Neurogenic vs. Vascular Claudication

Neurogenic Claudication: dermatomal distribution with positional relief occurring over minutes.

Vascular Claudication: sclerotomal distribution with relief occurring with rest over seconds.

Intradural Intramedullary Lesions

Syringomyelia

Definition

- cystic cavitation of the spinal cord
- presentation is highly variable, usually progresses over months to years
- initially pain and weakness; later atrophy and loss of pain and temperature sensation

Etiology

- 70% are associated with Chiari I malformation
- post-traumatic
- tumour

Clinical Features

- nonspecific features for any intramedullary spinal cord pathology:
 - sensory loss similar to central cord syndrome
 - pain and temperature loss with preserved touch and joint position sense in a cape-like distribution at level of cervical syrinx
 - dysesthetic pain often occurs in the distribution of the sensory loss
 - LMN arm/hand weakness or wasting
 - painless arthropathies (Charcot's joints), especially in the shoulder and neck due to loss of pain and temperature sensation (seen in less than 5%)

Investigations

- MRI is best method, myelogram with delayed CT

Treatment

- treat underlying cause (e.g. posterior fossa decompression for Chiari I, surgical removal of tumour if causing a syrinx)



Figure 23. T1 Weighted MRI of Syringomyelia



Spinal Cord Syndromes

Spinal Cord Injuries

- see Neurology, N4, for spinal cord anatomy

Complete Spinal Cord Lesion

- bilateral loss of motor/sensory and autonomic function at ≥ 4 segments below lesion/injury, with UMN signs
- about 3% of patients with complete injuries will develop some recovery within 24 hours, beyond 24 hours, no distal function will recover

Incomplete Spinal Cord Lesion

- any residual function at ≥ 4 segments below lesion
- signs include sensory/motor function in lower limbs and "sacral sparing" (perianal sensation, voluntary rectal sphincter contraction)

Table 13. Comparison between Incomplete Spinal Cord Lesion Syndromes

Syndrome	Etiology	Motor	Sensory
Brown-Séquard	Hemisection of cord	Ipsilateral LMN weakness at the lesion Ipsilateral UMN weakness below the lesion	Ipsilateral loss of vibration and proprioception Contralateral loss of pain and temperature Preserved light touch
Anterior Cord	Anterior spinal artery compression or occlusion	Bilateral LMN weakness at the lesion Bilateral UMN weakness below the lesion Urinary retention	Preserved vibration and proprioception Bilateral loss of pain and temperature Preserved light touch
Central Cord (most common)	Syringomyelia, tumours, spinal hyperextension injury	Bilateral motor weakness: Upper limb weakness (LMN lesion) greater than Lower limb weakness (UMN lesion) Urinary retention	Variable bilateral suspended sensory loss Loss of pain and temperature greater than loss of vibration and proprioception
Posterior Cord	Posterior spinal artery infarction, trauma	Preserved	Bilateral loss of vibration, proprioception, light touch at and below the lesion Preserved pain and temperature



Compartmentalize spinal cord syndromes anatomically by location.

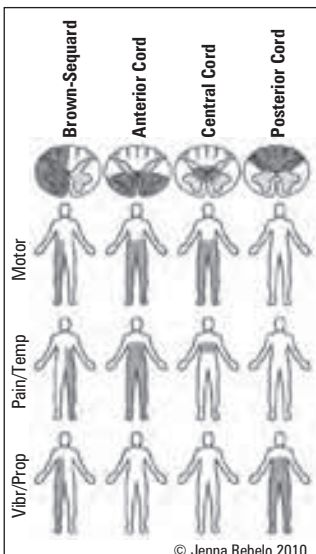


Figure 24. Spinal Cord Lesion Syndromes

Peripheral Nerves



- see [Neurology](#), N30

Classification and Clinical Course

- neurapraxia: axon intact but fails to function, recovery within hours to months
- nerve entrapment: nerve compressed by nearby anatomic structures, often secondary to localized, repetitive mechanical trauma with additional vascular injury to nerve → sensory loss in nerve distribution (often discriminative touch lost first)
- axonotmesis: axon disrupted but nerve sheath intact → Wallerian degeneration of axon segment distal to injury → axonal recovery of 1 cm/month, max at 1-2 years
- neurotmesis: nerve completely severed, need surgical repair for recovery

Investigations

- neurological exam (power, sensation, reflexes), localization via Tinel's sign (paresthesias elicited by tapping along the course of a nerve)
- electrophysiological studies (EMG, nerve conduction study) may be helpful in assessing nerve integrity and monitoring recovery, not helpful until 2-3 weeks post-injury
- labs: bloodwork, CSF
- imaging: C-spine, chest/bone x-rays, myelogram, CT, MRI "neurography" to rule out cerebral/spinal cord lesions, identify etiology
- angiogram if vascular damage is suspected

Treatment

- early neurosurgical consultation if injury is suspected
- entrapment
 - conservative: prevent repeated stress/injury, physiotherapy, NSAIDs, local anaesthesia/steroid injection
 - surgical: nerve decompression ± transposition for progressive deficits, muscle weakness/atrophy, failure of medical management
- stretch/contusion
 - follow-up clinically for recovery; exploration if no recovery in 3 months
- axonotmesis
 - if no evidence of recovery, resect damaged segment
 - prompt physical therapy and rehabilitation to increase muscle function, maintain joint range of motion, and maximize return of useful function
 - recovery usually incomplete
- neurotmesis
 - surgical repair of nerve sheath unless known to be intact [suture nerve sheaths directly if ends approximate or nerve graft (usually sural nerve)]
 - clean laceration: early exploration and repair
 - contamination or associated injuries: tag initially with nonabsorbable suture, reapproach within 10 days

Complications

- neuropathic pain: with neuroma formation
- complex regional pain syndrome: with sympathetic nervous system involvement

SPECIALTY TOPICS

Neurotrauma

Trauma Management (see also [Emergency Medicine](#), ER7)

Indications for Intubation in Trauma

1. depressed LOC (patient cannot protect airway): usually GCS ≤8
2. need for hyperventilation
3. severe maxillofacial trauma: patency of airway is doubtful
4. need for pharmacologic paralysis for evaluation or management
 - if basal skull fracture suspected, use orotracheal instead of nasotracheal intubation
 - note: intubation prevents patient's ability to verbalize for determining GCS



Glasgow Coma Scale

Eye Response	Verbal Response	Motor Response
4 spontaneous	5 oriented	6 obeys commands
3 opens eyes to voice	4 confused	5 localizes to pain
2 opens eyes to pain	3 inappropriate words	4 withdraws from pain
1 no eye opening	2 incomprehensible sounds	3 flexion to pain (decorticate posturing)
	1 no response	2 extension to pain (decerebrate posturing)
		1 no response



Assessment of Spine CT/X-ray (parasagittal view)

ABCDs

Alignment (Columns: anterior vertebral line, posterior vertebral line, spinolaminar line, posterior spinous line)
Bone (vertebral bodies, facets, spinous processes)
Cartilage
Disc (disc space and interspinous space)
Soft tissues



Which Patients Need CT Head or Transfer to a Neurosurgical Centre?

- Remains unconscious after resuscitation
- Focal neurological signs
- Deteriorating

Trauma Assessment

INITIAL MANAGEMENT

ABC's of Trauma Management

- see [Emergency Medicine](#), ER8

NEUROLOGICAL ASSESSMENT

Mini-History

- period of LOC, post traumatic amnesia, loss of sensation/function, type of injury/accident

Neurological Exam

- Glasgow Coma Scale (GCS)
- head and neck (lacerations, bruises, basal skull fracture signs, facial fractures, foreign bodies)
- spine (palpable deformity, midline pain/tenderness)
- eyes (pupillary size and reactivity)
- brainstem (breathing pattern, CN palsies)
- cranial nerve exam
- motor exam, sensory exam (only if GCS is 15), reflexes
- sphincter tone
- record and repeat neurological exam at regular intervals

Investigations

- spinal injury precautions (cervical collar) are continued until c-spine is cleared
- C,T,L-spine x-rays
 - AP, lateral, odontoid views for C-spine (must see from C1 to T1 (swimmer's view if necessary) or CT
 - rarely done: oblique views looking for pars interarticularis fracture ("Scottie dog" sign)
- CT head and upper C-spine (whole C-spine if patient unconscious) look for fractures, loss of mastoid or sinus air spaces, blood in cisterns, pneumocephalus
- cross and type, ABG, CBC, drug screen (especially alcohol)
- chest and pelvic x-ray as indicated

TREATMENT

Treatment for Minor Head Injury

- see Canadian CT Head Rule sidebar, [Emergency Medicine](#), ER8
- observation over 24-48 hours
- wake every hour
- judicious use of sedatives or pain killers during monitoring period

Treatment for Severe Head Injury (GCS ≤ 8)

- clear airway and ensure breathing (if GCS ≤ 8 , intubate)
- secure C-spine
- maintain adequate BP
- monitor to detect complications (GCS, CT, ICP)
- monitor and manage increased ICP if present (see *Herniation Syndromes*, NS6)

Which patients should be admitted to hospital?

- skull fracture
- indirect signs of basal skull fracture
- confusion, impaired consciousness
- focal neurological signs
- extreme headache, vomiting
- seizures
- concussion with >5 minutes amnesia
- unstable spine
- use of alcohol
- poor social support (i.e. no friend/relative to monitor for next 24 hours)
- if there is any doubt, especially with children

KEY POINTS

- **never do lumbar puncture in head injury** unless increased ICP has been ruled out
- all patients with head injury have C-spine injury until proven otherwise
- alcohol may not be the cause of coma – there may also be a hematoma
- low BP after head injury means injury elsewhere
- must clear spine both radiologically AND clinically (will require re-assessment if/when patient improves clinically)

Head Injury

Epidemiology

- male to female: 2-3:1

Pathogenesis

- acceleration/deceleration: contusions, subdural hematoma, axon and vessel shearing/mesencephalic hematoma
- impact: skull fracture, concussion, epidural hematoma
- penetrating: worse with high velocity and/or high missile mass
 - low velocity: highest damage to structures on entry/exit path
 - high velocity: highest damage away from missile tract

Scalp Injury

- rich blood supply
- considerable blood loss (vessels contract poorly when ruptured)
- minimal risk of infection due to rich vascularity

Skull Fractures

- depressed fractures: double density on skull x-ray (outer table of depressed segment below inner table of skull), CT with bone windows is gold standard
- simple fractures (closed injury): no need for antibiotics, no surgery
- compound fractures (open injury): increased risk of infection, surgical debridement within 24 hours is necessary
 - internal fractures into sinus may lead to meningitis, pneumocephalus
 - risk of operative bleed may limit treatment to antibiotics
- basal skull fractures: not readily seen on x-ray, rely on clinical signs
 - retroauricular ecchymoses (Battle's sign)
 - periorbital ecchymoses (raccoon eyes)
 - hemotympanum
 - CSF rhinorrhea, otorrhea (suspect CSF if halo or target sign present); suspect with Lefort II/III midface fracture

Cranial Nerve Injury

- most traumatic causes of cranial nerve injury do not warrant surgical intervention
- surgical intervention
 - CN II – local eye/orbit injury
 - CN III, IV, VI – if herniation secondary to mass
 - CN VIII – repair of ossicles
- CN injuries that improve
 - CN I – recovery may occur in a few months; most do not improve
 - CN III, IV, VI – majority recover
 - CN VII – recovery with delayed lesions
 - CN VIII – vestibular symptoms improve over weeks, deafness usually permanent (except when resulting from hemotympanum)

Arterial Injury

- e.g. carotid-cavernous (C-C) fistula, carotid/vertebral artery dissection

Intracranial Bleeding

(see *Blood*, NS15 and *Cerebrovascular Disease*, NS17)

Brain Injury

Primary Impact Injury

- mechanism of injury determines pathology: penetrating injuries, direct impact
 - low velocity: local damage
 - high velocity: distant damage possible (due to wave of compression), concussion
- concussion**: a trauma-induced alteration in mental status
 - American Academy of Neurology (AAN) Classification (see sidebar)
 - no parenchymal abnormalities on CT
- coup** (damage at site of blow)
- contre-coup** (damage at opposite site of blow)
 - acute decompression causes cavitation followed by a wave of acute compression



Head Injury can involve:
Scalp, Skull, Meninges, Brain



Etiologies

- MVA (30-55%)
- Falls (15-35%)
- Gun Shot Wound (5-20%)



Layers of Scalp

SCALP

Skin
Connective tissue (dense)
Aponeurosis (galea)
Loose connective tissue
Periosteum



AAN Classification

Grade 1: altered mental status < 15 min
Grade 2: altered mental status > 15 min
Grade 3: any loss of consciousness


Management Associated with AAN Concussion Grades

AAN Grade	Management Options
1	<ul style="list-style-type: none"> Examine 15 min for amnesia and other symptoms Return to normal activity if symptoms clear within 15 mins
2	<ul style="list-style-type: none"> Remove from activity for 1 day, then reexamine CT or MRI if H/A or other symptoms worsen or last > 1 week Return to normal activity after 1 week without symptoms
3	<ul style="list-style-type: none"> Emergent neuro exam + imaging; if initial exam is normal, may go home with close follow up Admit if any signs of pathology or persistent abnormal mental status CT or MRI if H/A or other symptoms If brief concussion (< 1 min), return to normal activity after 1 week without symptoms If prolonged concussion (> 1 min), return to normal activity only after 2 weeks without symptoms



SIADH → hyponatremia
DI → hypernatremia

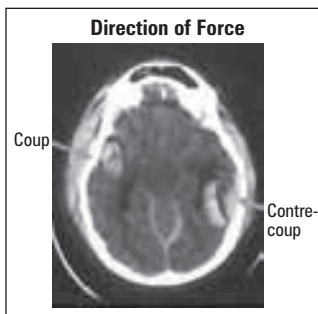


Figure 25. CT Showing Coup-Contre-Coup Injury

- contusion (hemorrhagic)
 - high density areas on CT ± mass effect
 - commonly occurs with brain impact on bony prominences (inferior frontal lobe, pole of temporal lobe)
- diffuse axonal injury/shearing
 - wide variety of damage results
 - may tear blood vessels (hemorrhagic foci)
 - often the cause of decreased LOC if no space occupying lesion on CT

Secondary Pathologic Processes

- same subsequent biochemical pathways for each traumatic etiology
- delayed and progressive injury to the brain due to
 - high glutamate release → NMDA → cytotoxic cascade
 - cerebral edema
 - intracranial hemorrhages
 - ischemia/infarction
 - raised ICP, intracranial HTN
 - hydrocephalus

Extracranial Conditions

- hypoxemia
 - due to trauma to the chest, upper airway, brainstem
 - extremely damaging to vulnerable brain cells
 - leads to ischemia, raised ICP
- hypercarbia
 - leads to raised ICP (secondary to vasodilation)
- systemic hypotension
 - caused by blood loss (e.g. ruptured spleen)
 - loss of cerebral autoregulation leads to decreased CPP, ischemia
- hyperpyrexia
 - leads to increased brain metabolic demands → ischemia
- fluid and electrolyte imbalance
 - iatrogenic (most common)
 - SIADH caused by head injury
 - diabetes insipidus (DI) from head injury
 - may lead to cerebral edema and raised ICP
- coagulopathy

Intracranial Conditions

- raised ICP due to traumatic cerebral edema OR traumatic intracranial hemorrhage

Brain Injury Outcomes

- mildly traumatic (GCS 13-15): post-concussive symptoms: H/A, fatigue, dizziness, nausea, blurred vision, diplopia, memory impairment, tinnitus, irritability, low concentration; 50% at 6 weeks, 14% at 1 year
- moderately traumatic (GCS 9-12): proportional to age (>40) and CT findings; 60% good recovery, 26% moderately disabled, 7% severely disabled, 7% vegetative/dead
- severe (GCS ≤8): difficult to predict, correlates with post-resuscitation GCS (especially motor) and age

Late Complications of Head/Brain Injury

- seizures: 5% of head injury patients develop seizures
 - incidence related to severity and location of injury (increased with local brain damage or intracranial hemorrhage)
 - post-traumatic seizure may be immediate, early, or late
 - presence of early (within first week) post-traumatic seizure raises incidence of late seizures
- meningitis: associated with CSF leak from nose or ear
- hydrocephalus: acute hydrocephalus or delayed normal pressure hydrocephalus (NPH)

Spinal Cord Injury (SCI)



- see Orthopaedics, OR22 and Emergency Medicine, ER9

Neurogenic and Spinal Shock

1. neurogenic shock: hypotension that follows SCI (SBP usually ≤ 80 mmHg) caused by
 - interruption of sympathetics (unopposed parasympathetics) below the level of injury
 - loss of muscle tone due to skeletal muscle paralysis below level of injury \rightarrow venous pooling (relative hypovolemia)
 - blood loss from associated wounds (true hypovolemia)
2. spinal shock: transient loss of all neurologic function below the level of the spinal cord injury, causing flaccid paralysis and areflexia for variable periods

Whiplash-Associated Disorders

- definition: traumatic injury to the soft tissue structures in the region of the cervical spine due to hyperflexion, hyperextension or rotational injury to the neck

Initial Management of SCI

- major causes of death in SCI are aspiration and shock
- the following patients should be treated as having a SCI until proven otherwise:
 - all victims of significant trauma
 - minor trauma patients with decreased LOC or complaints referable to neck or back pain or SCI (weakness, abdominal breathing, numbness/tingling, priapism)

Stabilization and Initial Evaluation in the Hospital

1. ABC's
2. immobilization: maintain backboard/head-strap and use log-rolling during transfers
3. hypotension: maintain sBP ≥ 90 mmHg with
 - pressors if necessary: dopamine is agent of choice (avoid phenylephrine – causes reflex bradycardia)
 - hydration (cautiously to prevent pulmonary edema)
 - atropine (for bradycardia associated with hypotension)
4. oxygenation
5. NG tube to suction: prevents N/V, decompresses abdomen to facilitate breathing
6. foley catheter to urometer (to monitor ins and outs)
7. DVT prophylaxis
8. temperature regulation
9. monitor CBC/electrolytes
10. focused history
 - mechanism of injury (hyperflexion, extension, axial loading, etc.)
 - weakness/numbness/tingling in extremities
11. palpate spine for
 - point tenderness
 - a "step-off" deformity
 - widened interspinous space
12. motor level assessment – grade with American Spinal Injury Association (ASIA) Standards
 - skeletal muscle exam
 - rectal exam for voluntary anal sphincter contraction
13. sensory level assessment (grade with ASIA Standards)
 - sensation to pinprick (spinothalamic tract)
 - sensation in face (spinal trigeminal tract can sometimes descend as low as C4)
 - sensation to light touch (anterior spinothalamic tract in anterior cord)
 - proprioception (posterior columns)
14. evaluation of reflexes
15. signs of autonomic dysfunction: altered levels of perspiration, bowel or bladder incontinence, priapism
16. radiographic evaluation
 - 3 view C-spine x-rays (AP, lateral and odontoid) to adequately visualize C1 to C7-T1 junction
 - oblique views to assess integrity of articular masses and lamina
 - flexion-extension views to disclose occult instability
 - CT scan (bony injuries) \pm MRI (soft tissue injuries)

Medical Management Specific to SCI

- methylprednisolone (given within 8 hours of injury)
- \pm decompression in acute, nonpenetrating SCI (Fehlings and Tator, 1999)

Does early decompression improve neurological outcome of spinal cord injured patients?

Appraisal of the literature using a meta-analytical approach

Spinal Cord 2004; 42:503-512.

Introduction: This study was aimed at determining whether neurological outcome was improved with early (< 24 hours) spinal decompression surgery as compared to either late (> 24 hours) surgery or conservative management.

Methods/Population: A Medline search found 37 articles with a total of 1683 eligible patients (traumatic spinal injury), 919 with complete paralysis and 764 with an 'incomplete' neurological deficit. Outcome was determined by calculating the percentage of patients with sensory or motor function improvement according to the Frankel's scale.

Results: Early decompression resulted in improved outcome compared to both late and conservative treatments, for both complete and incomplete injury ($p < 0.001$ each respectively). A homogeneity assessment amongst studies revealed that patients undergoing early decompression for incomplete injury was homogenous ($p > 0.05$), however all other subgroups showed significant heterogeneity.

Conclusion: Although statistically promising, with the lack of patient homogeneity in recent studies, the current recommendation is that early surgical decompression be considered as an optional practice following traumatic spinal cord injuries.

Methylprednisolone treatment in acute spinal cord injury: the myth challenged through a structured analysis of published literature

The Spine Journal 2006; 16:335-343

Introduction: Beginning in the late 70's and through to the early 90's the National Acute Spinal Cord Injury Studies (NASCIS) were conducted in three large randomized controlled trials, and from those trials the recommendation to give patients methylprednisolone (MP) within 8 hours of spinal injury. Critical evaluation of each of these trials over the years led these authors to assess the literature (including the NASCIS trials) to re-evaluate the evidence behind this recommendation.

Methods/Population: A critical appraisal of the data obtained through the NASCIS studies along with a literature review of other trials investigating the effect of MP on acute spinal injury.

Results: The authors raise several important issues with each of NASCIS II and III, including the fact that statistical analysis was completed on only 30% of the population in NASCIS II and benefits were only observed in 'incomplete' spinal injuries. NASCIS III was evaluated for lack of explanation on optimum MP timing along with failure to report motor changes post-therapy on both the right and left side of the body, suggesting that changes in one side were not significant, arguing against the meaningfulness of the results. Other prior studies failed to reproduce the results of NASCIS, but there is the confounding factor that studies since NASCIS have all included MP since it was thought to be unethical to randomize individuals to a placebo group.

Conclusion: The authors conclude that based on these and other major criticisms of the NASCIS II and III, many neurosurgical departments have stopped using MP as a standard routine in acute spinal cord injury, and also note that its use is not currently recommended by the Food and Drug Administration in the United States. They suggest further investigation is warranted to answer this question conclusively.

Fractures of the Spine

Fractures and Fracture-Dislocations of the Thoracic, Thoracolumbar and Lumbar Spine

- assess ligamentous instability using flexion/extension x-ray views of C-spine ± MRI
- thoracolumbar spine unstable if 4/6 segments disrupted (3 columns divided into left and right)
 - anterior column: anterior half of vertebral body, disc and anterior longitudinal ligament
 - middle column: posterior half of vertebral body, disc and posterior longitudinal ligament
 - posterior column: posterior arch, facet joints, pedicle, lamina and supraspinous, interspinous and ligamentum ligaments

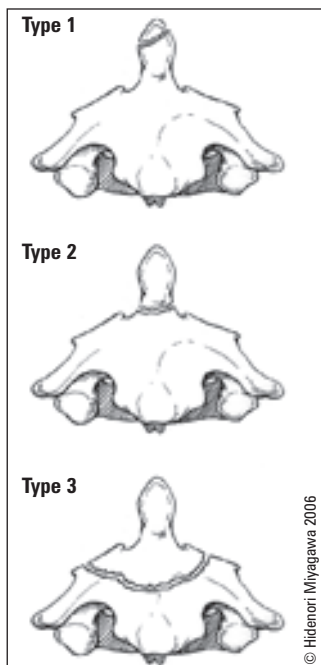


Figure 26. Odontoid Fracture Classification

Types of Injury (Dennis Classification)

- compression fracture (58%)
 - produced by flexion
 - posterior ligament complex (supraspinous and interspinous ligaments, ligamentum flavum and intervertebral joint capsules) remain intact
 - fractures are stable but lead to kyphotic deformity
- burst fracture (17%)
 - stable: anterior and middle columns parted with bone retropulsed nearby
 - ♦ hallmark is pedicle widening on AP X-ray
 - ♦ spinal cord (seen on x-ray and CT); posterior column is uninjured
 - unstable: same as the stable but with posterior column disruption (usually ligamentous)
- flexion distraction injury (6%)
 - hyperflexion and distraction of posterior elements
 - ♦ middle and posterior columns fail in distraction
 - classic: Chance = horizontal fracture through posterior arch, pedicles, posterior vertebral body
 - can be purely ligamentous, i.e. through PLL and disc
- fracture-dislocation (6%)
 - anterior and cranial dislocation of superior vertebral body → 3 column failure
 - three types:
 - ♦ flexion-rotation
 - ♦ flexion-distraction
 - ♦ shear/hyperextension (rare)

Fractures of the Cervical Spine

Types of Injury

- C1 vertebral fracture (Jefferson fracture)
 - vertical compression forces the occipital condyles of the skull down on the C1 vertebra (atlas), pushing the lateral masses of the atlas outward and disrupting the ring of the atlas
 - also can cause an occipital condylar fracture
- odontoid process fracture
 - causes C1 and odontoid of C2 to move independently of C2 body
 - this occurs because
 - ♦ normally C1 vertebra and odontoid of C2 are a single functional unit
 - ♦ alar and transverse ligaments on posterior aspect of odontoid most commonly remain intact following injury
 - patients often report a feeling of instability and present holding their head with their hands
- C2 vertebral fracture (hangman fracture, traumatic spondylolisthesis of axis):
 - ♦ bilateral fracture through the pars interarticularis of C2 with subluxation of C2 on C3
 - ♦ usually neurologically intact
- clay shoveler's fracture
 - avulsion of spinous process, usually C7

Imaging

- AP spine x-ray (open-mouth and lateral view), CT

Treatment

- immobilization in cervical collar or halo vest until healing occurs, (usually 2-3 months)
- Type II and III odontoid fractures
 - consider surgical fixation for comminution, displacement or inability to maintain alignment with external immobilization
 - confirm stability after recovery with flexion-extension x-rays

Neurologically Determined Death



Definition

- irreversible and diffuse brain injury resulting in absence of clinical brain function
- cardiovascular activity may persist for up to two weeks

Criteria of Diagnosis

- prerequisites: no CNS depressant drugs/neuromuscular blocking agents, no drug intoxication/poisoning, temperature $>32^{\circ}\text{C}$, no electrolyte/acid-base/endocrine disturbance
- absent brainstem reflexes:
 - absent pupillary light reflex
 - absent corneal reflexes
 - absent oculocephalic response
 - absent caloric responses (e.g. no deviation of eyes to irrigation of each ear with 50 cc of ice water – allow 1 min after injection, 5 min between sides)
 - absent pharyngeal and tracheal reflexes
 - absent cough with tracheal suctioning
 - absent respiratory drive at $\text{PaCO}_2 >60$ mmHg or >20 mmHg above baseline (apnea test)
- 2 evaluations separated by time, usually performed by two specialists (e.g. anesthetist, neurologist, neurosurgeon)
- confirmatory testing: flat EEG, absent perfusion assessed with cerebral angiogram

Altered Level of Consciousness

Evaluation of Patient

History

- previous/recent head injury (hematoma)
- sudden collapse (ICH, SAH)
- cardiovascular surgery, prolonged cardiac arrest (hypoxia)
- limb twitching, incontinence, tongue biting (seizure, post-ictal state)
- recent infection (meningitis)
- other medical problems (diabetes mellitus, renal failure, hepatic encephalopathy)
- psychiatric illness (drug overdose)
- telephone witnesses, read ambulance report, check for medic-alert bracelet
- neurologic symptoms (headache, visual changes, focal weakness)

Physical Examination

- Glasgow Coma Scale (see sidebar, *Neurotrauma*, NS30)
- pupils: reactivity and symmetry, papilledema (increased ICP)
- reflexes:
 - corneal reflex: normal = bilateral blinking response
 - gag reflex: normal = gag
 - oculocephalic reflex (doll's eye): normal = eyes move in opposite direction of head, as if trying to maintain fixation of a point
 - vestibulocochlear response (cold caloric): normal = nystagmus fast phase away from stimulated ear
 - deep tendon reflexes
 - plantar reflexes: normal = flexor plantar response
- tone
- spontaneous involuntary movements
- assess for meningeal irritation, increased temperature
- assess for head injury, Battle's sign, raccoon eyes, skin rashes, and joint abnormalities that may suggest vasculitis



Caloric Reflexes

COWS

Cold
Opposite
Warm
Same

Coma

Definition

- an unrousable state in which patients show no meaningful response to environmental stimuli

Pathophysiology

- lesions affecting the cerebral cortex bilaterally, the reticular activating system (RAS) or their connecting fibres
- focal supratentorial lesions do not alter consciousness except by herniation (compression on the brainstem or on the contralateral hemisphere) or by precipitating seizures

Classification

- structural lesions (tumour, pus, blood, infarction, CSF): 1/3 of comas
 - supratentorial mass lesion – leads to herniation
 - infratentorial lesion – compression of or direct damage to the RAS or its projections
- metabolic disorders/diffuse hemispheric damage: 2/3 of comas
 - deficiency of essential substrates (e.g. oxygen, glucose, vitamin B₁₂)
 - exogenous toxins (e.g. drugs, heavy metals, solvents)
 - endogenous toxins/systemic metabolic diseases (e.g. uremia, hepatic encephalopathy, electrolyte imbalances, thyroid storm)
 - infections (meningitis, encephalitis)
 - trauma (concussion, diffuse shear axonal damage)

Investigations and Management

- ABCs
- labs: electrolytes, TSH, LFTs, Cr, BUN, Ca, Mg, PO₄, toxin screen, glucose
- CT/MRI, LP, EEG

Persistent Vegetative State

Definition

- a condition of complete unawareness of the self and the environment accompanied by sleep-wake cycles with either complete or partial preservation of hypothalamic and brainstem autonomic function
- “awake but not aware”
- follows comatose state

Etiology/Prognosis

- most commonly caused by cardiac arrest or head injury
- due to irreversible loss of cerebral cortical function BUT intact brainstem function
- average life expectancy is 2-5 years

Pediatric Neurosurgery

Spinal Dysraphism

SPINA BIFIDA OCCULTA

Definition

- congenital absence of a spinous process and a variable amount of lamina
- no visible exposure of meninges or neural tissue

Epidemiology

- 15-20% of the general population; most common at L5 or S1

Etiology

- failure of fusion of the posterior neural arch

Clinical Features

- no obvious clinical signs
- presence of lumbosacral cutaneous abnormalities (dimple, sinus, port-wine stain, or hair tuft) should increase suspicion of an underlying anomaly (lipoma, dermoid, diastatomyelia)

Investigations

- plain film – absence of the spinous process along with minor amounts of the neural arch
- U/S or MRI to exclude spinal anomalies

Treatment

- requires no treatment

MENINGOCELE (SPINA BIFIDA APERTA)

Definition

- herniation of meningeal tissue and CSF through a defect in the spine, without associated herniation of neural tissue

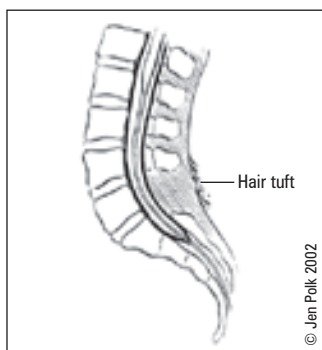


Figure 27. Spina Bifida Occulta

Etiology

- primary failure of neural tube closure

Clinical Features

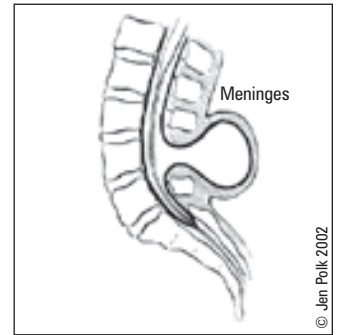
- most common in lumbosacral area
- usually no disability, low incidence of associated anomalies and hydrocephalus

Investigations

- plain films, CT, MRI, U/S, echo, genitourinary (GU) investigations

Treatment

- surgical excision and tissue repair (excellent results)

**Figure 28. Meningocele****MYELOMENINGOCELE****Definition**

- herniation of meningeal and CNS tissue through a defect in the spine

Etiology

- same as meningocele

Clinical Features

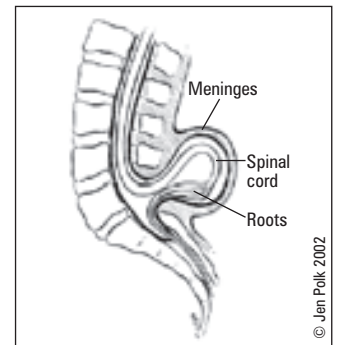
- sensory and motor changes distal to anatomic level producing varying degrees of weakness
- urinary and fecal incontinence
- 65-85% of patients with myelomeningocele have hydrocephalus
- most have Type II Chiari malformation, see NS38

Investigations

- plain films, CT, MRI, U/S, echo, GU investigations

Treatment

- surgical closure to preserve neurologic status and prevent CNS infections

**Figure 29. Myelomeningocele****Prognosis**

- operative mortality close to 0%, 95% 2-year survival
- 80% have IQ >80 (but most are 80-95), 40-85% ambulatory, 3-10% have normal urinary continence
- early mortality usually due to Chiari malformation complications (respiratory arrest and aspiration), whereas late mortality is due to shunt malfunction

Intraventricular Hemorrhage (IVH)

- see [Pediatrics](#), P74

Hydrocephalus in Pediatrics**Etiology**

- congenital
 - aqueductal anomalies, primary aqueductal stenosis in infancy
 - secondary gliosis due to intrauterine viral infections (mumps, varicella, TORCH)
 - Dandy-Walker malformation (2-4%)
 - Chiari malformation, especially Type II
 - myelomeningocele
- acquired
 - post meningitis
 - post hemorrhage (SAH, IVH)
 - masses (vascular malformation, neoplastic)

Clinical Features

- symptoms and signs of hydrocephalus are age related in pediatrics
- increased head circumference (HC), bulging anterior fontanelle, widened cranial sutures
- irritability, lethargy, poor feeding and vomiting
- "cracked pot" sound on cranial percussion
- scalp vein dilation (increased collateral venous drainage)
- sunset sign – forced downward deviation of eyes
- episodic bradycardia and apnea

Investigations

- skull x-ray, U/S, CT, MRI, ICP monitoring

Treatment

- similar to adults (see *Hydrocephalus*, NS7)

Dandy-Walker Malformation

Definition

- atresia of foramina of Magendie and Luschka, resulting in
 - complete or incomplete agenesis of the cerebellar vermis with widely separated, hypoplastic cerebellar hemispheres
 - posterior fossa cyst, enlarged posterior fossa
 - dilatation of 4th ventricle (also 3rd and lateral ventricles)
- associated anomalies
 - hydrocephalus (90%)
 - agenesis of corpus callosum (17%)
 - occipital encephalocele (7%)

Epidemiology

- 2-4% of pediatric hydrocephalus

Clinical Features

- 20% are asymptomatic, seizures occur in 15%
- symptoms and signs of hydrocephalus combined with a prominent occiput in infancy
- ataxia, spasticity, poor fine motor control common in childhood

Investigations

- ultrasound, CT, MRI

Treatment

- asymptomatic patients require no treatment
- associated hydrocephalus requires surgical treatment
 - supratentorial lateral ventricular or cystoperitoneal shunt

Prognosis

- 75-100% survival, 50% have normal IQ

Chiari Malformations

Definition

- malformations at the medullary-spinal junction

Etiology

- unclear, likely maldevelopment/dysgenesis during fetal life

Categories

- Type I (cerebellar ectopia)
 - definition: cerebellar tonsils lie below the level of the foramen magnum
 - epidemiology: average age at presentation 15 years
 - clinical features:
 - ♦ many are asymptomatic
 - ♦ scoliosis
 - ♦ brain compression
 - ♦ central cord syndrome (65%)
 - ♦ syringomyelia (50%)
 - ♦ foramen magnum compression syndrome (22%)
 - ♦ cerebellar syndrome (11%)
 - ♦ hydrocephalus (10%)
- Type II
 - definition: part of cerebellar vermis, medulla and 4th ventricle extend through the foramen magnum often to midcervical region
 - epidemiology: present in infancy
 - clinical features: findings due to brainstem and lower cranial nerve dysfunction
 - syringomyelia, hydrocephalus in >80%

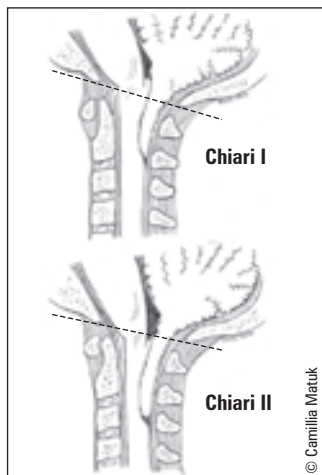


Figure 30. Chiari Malformations

Investigations

- MRI or CT myelography

Treatment

- indications for surgical decompression
 - Type I: symptomatic patients (early surgery recommended; <2 years post symptom onset) → suboccipital craniectomy, duroplasty
 - Type II: neurogenic dysphagia, stridor, apneic spells → cervical laminectomy, duraplasty

Craniosynostosis

Definition

- premature closure of the cranial suture(s)

Classification

- sagittal (most common): long narrow head with ridging sagittal suture (scaphocephaly)
- coronal: expansion in superior and lateral direction (brachiocephaly)
- metopic (trigonocephaly)
- lambdoid: least common

Epidemiology

- 0.6/1,000 live births, most cases are sporadic; familial incidence is 2% of sagittal and 8% of coronal synostosis

Clinical Features

- skull deformity, raised ICP, ± hydrocephalus
- ophthalmologic problems due to increased ICP or bony abnormalities of the orbit

Investigations

- plain radiographs, CT scan

Treatment

- parental counseling about nature of deformity, associated neurological symptoms
- surgery for cosmetic purposes, except in cases of elevated ICP (≥2 sutures involved)

Pediatric Brain Tumours

- see also *Tumour*, NS9

Epidemiology

- 20% of all pediatric cancers (second only to leukemia)
- 60% of pediatric brain tumours are infratentorial
- pediatric brain tumours arise from various cellular lineages
 - glia: low-grade astrocytoma (supra- or infratentorial), anaplastic astrocytoma, glioblastoma multiforme (largely supratentorial) (see *Astrocytoma*, NS11 for details)
 - primitive nerve cells: supratentorial [primitive neuroectodermal tumour (PNET)]
 - ♦ 90% of neonatal brain tumours, infratentorial (medulloblastoma), pineal gland (pineoblastoma)
 - non-neuronal cells: germ cell tumour, craniopharyngioma, dermoid, meningioma, neurinoma, pituitary adenoma, others

Clinical Features

- vomiting, seizure, macrocrania, hydrocephalus
- developmental delay, poor feeding, failure to thrive
- often initially escape diagnosis due to expansile cranium and neural plasticity in children

Relative Frequency of Pediatric Brain Tumours

Tumour type	Percent (%)
Astrocytoma, low-grade	40
Supratentorial	(23)
Infratentorial	(17)
Medulloblastoma	20
Brainstem glioma	8
Ependymoma	8
Malignant glioma	6
Craniopharyngioma	6
PNET	4
Pineal, germ cell tumour	3
Other	5

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Functional Neurosurgery

Movement Disorders

- see *Parkinson's Disease*, *Tremor*, *Dystonia*, and *Multiple Sclerosis* sections in Neurology, N27, N26, N28, N49, respectively

Table 14. Surgical Targets for Movement Disorders

Disorder	Indications	Procedures	Outcomes	Morbidity
Parkinson's Disease	Intractable contralateral bradykinesia/tremor Failure of medical management (advanced disease) Drug-induced dyskinesias (see dystonia, below)	Simultaneous, bilateral surgery/stimulation is most common Preferred target: anterodorsal subthalamic nucleus (STN) Other targets: stereotactic ablation (pallidotomy)/stimulation of posteroventral globus pallidus interna (GPi) Caudal zona incerta Parkinsonian tremor: stereotactic ablation (thalamotomy)/stimulation of ventral intermediate (Vim) nucleus of thalamus	39-48% improvement in Unified Parkinson's Disease Rating Scale (UPDRS) scores Reduced dosage of medications (STN) More effective than medical management in advanced PD Early intervention may reduce severity, course, and progression of disease Of little benefit for patients with atypical presentations	Intracerebral hemorrhage, infection, seizure (1%-4%) Paresthesias Involuntary movements Cognitive functioning: decreased lexical fluency, impaired executive function (STN > GPi) Psychiatric: depression, mania, anxiety, apathy (STN > GPi)
Dystonia	Contralateral primary (generalized) dystonias; cervical and tardive dystonias (GPi) Contralateral secondary dyskinesia (i.e. drug-induced: L-dopa, neuroleptics; STN)	Preferred target (primary dystonia): stereotactic ablation (pallidotomy)/stimulation of posteroventral GPi Secondary dystonia: stimulation of anterodorsal STN Stimulation of ventral posterior lateral thalamic nucleus (VPL)	Primary dystonia: 51% reduction in Burke-Fahn-Marsden Dystonia Scale (BFMDs) score Secondary dystonia: 62-89% improvement in dystonias Delayed effects: weeks → months	Intracerebral hemorrhage, infection, seizure (1%-4%) Minor effects on cognitive functioning (esp. decreased lexical fluency; STN > GPi)
Tremor	Contralateral appendicular ET (first disorder to be treated by DBS; DBS is viable alternative to Rx) Intention (cerebellar) tremor (IT) resulting from demyelination of cerebellar outflow tracts (i.e. in multiple sclerosis) Brainstem tremor (Holmes tremor)	Preferred target: stereotactic ablation (thalamotomy)/stimulation of Vim nucleus of thalamus Other targets: stimulation of caudal zona incerta Parkinsonian tremor: stimulation of anterodorsal STN	Durable reductions in essential tremor rating scale (ETRS) scores Reduced dosage of medications Conflicting data on vocal/facial tremor	Intracerebral hemorrhage, infection, seizure (1%-4%) Paresthesias/pain Dysarthria Ataxia Minor effects on cognitive functioning (esp. decreased lexical fluency) Tolerance may develop over time

Neuropsychiatric Disorders

- see *Tourette's Syndrome*, *Obsessive Compulsive Disorder* and *Depression* sections in Neurology, N29 and Psychiatry, PS15, PS7

Table 15. Surgical Targets for Neuropsychiatric Disorders

Disorder	Indications	Procedures	Outcomes	Morbidity
Obsessive Compulsive Disorder (OCD)	Severe symptoms refractory to medical management	Anterior capsulotomy/stimulation of the anterior limb of the internal capsule (IC)	Currently under investigation Reportedly 25-75% response rate	Intracerebral hemorrhages (1%-2%) Mild effects on cognitive functioning Anxiety ± panic disorder (case report)
Tourette's Syndrome	Severe symptoms refractory to medical management	Stimulation of midline intralaminar nuclei of the thalamus Stimulation of motor and limbic portions of GPi Stimulation of the anterior limb of the IC	Currently under investigation Reportedly > 70% reduction in vocal or motor tics + urge	Intracerebral hemorrhages (1%-2%) Mild sexual dysfunction
Major Depressive Disorder (MDD)	Severe depression refractory to medical management and ECT	Stimulation of the subgenual cingulate cortex	Currently under investigation Reportedly 60% response rate; 35% remission rate	Intracerebral hemorrhages (1%-2%) Pain, headache Worsening mood, irritability

Chronic Pain

Table 16. Surgical Targets for Chronic Pain

Disorder	Indications	Procedures	Outcomes	Morbidity
Neuropathic Pain	Severe, intractable, organic neuropathic pain (i.e. post-stroke pain, phantom limb pain, trigeminal neuralgia, chronic low-back pain, complex regional pain syndrome)	Preferred target: stimulation of the contralateral ventral posterior lateral (VPL) and medial (VPM) thalamic nuclei \pm periventricular/periaqueductal grey matter (PVG/PAG) Other targets: stimulation of the contralateral IC Stimulation of the contralateral motor cortex	47% improvement in perception of pain intensity Less favourable results in central pain syndromes and poorly localized pain	Intracerebral hemorrhages (1%-2%) Paraesthesia Anxiety \pm panic disorder
Nociceptive Pain	Severe, intractable, organic nociceptive pain	Bilateral (most common) stimulation of the PVG/PAG	Reportedly 63% improvement in perception of pain intensity	Intracerebral hemorrhages (1%-2%) Paraesthesia Anxiety \pm panic disorder

Surgical Management of Epilepsy

Neurosurgical Treatment of Epilepsy

- see Neurology, N8 for the medical treatment of epilepsy

Indications

- medically refractory seizures, usually defined as seizures resistant to two first line anti-seizure medications used in succession
- identification of a distinct epileptogenic region through clinical history, EEG, MRI, and neuropsychological testing. Other localizing investigations include magnetoencephalography, SPECT and PET
- if a distinct epileptogenic region cannot be identified, the patient may be a candidate for a palliative procedure such as corpus callosotomy

Procedure

- most commonly
 - adults: resection of the hippocampus and parahippocampal gyrus for mesial temporal lobe epilepsy arising from mesial temporal sclerosis
 - children: resection of an epileptogenic space-occupying lesion
- hemispherectomy and corpus callosotomy are less common

Outcomes and Goals

- freedom from seizures
- 41-79% of adult patients are seizure free for 5 years after temporal lobe resection
- 58-78% of children are seizure free after surgery
- surgery is associated with improvements in preexisting psychiatric conditions such as depression and anxiety, as well as improvement in quality of life measures

Morbidity

- 0.4-4% of surgical patients will have partial hemianopsia, aphasia, motor deficit, sensory deficit, or cranial nerve palsy following anterior mesial temporal lobectomies
- most patients will have some decline in verbal memory following dominant temporal lobectomy and in visuospatial memory in non-dominant temporal resection
- the degree of memory decline stabilizes after 1-2 years

Predictors

- positive predictive factors for seizure freedom following anteromedial temporal lobe resection
 - hippocampal sclerosis (unilateral)
 - focal localization of interictal epileptiform discharges
 - absence of preoperative generalized seizures
 - tumoural cause
 - complete resection of the lesion

A Randomized, Controlled Trial of Surgery for Temporal-lobe Epilepsy

NEJM 2001; 345:311-8

This randomized control trial evaluates the efficacy and safety of neurosurgery for temporal lobe epilepsy.

Methods: 80 patients with poorly controlled temporal-lobe epilepsy were randomized for surgery (n=40) or for continued treatment with antiepileptic drugs (n=40). The primary outcome was freedom from seizures that impair awareness of self and surroundings during the period of 1 year. Secondary outcomes included frequency and severity of seizures, quality of life, disability and death.

Conclusions: In patients with poorly controlled temporal-lobe epilepsy, surgery is superior to prolonged medical therapy.

Surgical Management for Trigeminal Neuralgia

Medical Therapy for Trigeminal Neuralgia

- see Neurology, N18 for medical management

Surgical Therapy for Trigeminal Neuralgia

- reserved for cases refractory to medical management

Surgical Options

- trigeminal nerve branch procedures
 - local blocks (phenol, alcohol)
 - neurectomy of the trigeminal branch
- nerve branches
 - V₁ at the supraorbital, supratrochlear or infraorbital nerves
 - V₂ at the foramen rotundum
 - V₃ block at the foramen ovale
- percutaneous trigeminal rhizotomy
 - glycerol injection
 - mechanotrauma via catheter balloon
 - injection of sterile boiling water
- radiofrequency thermocoagulation
- microvascular decompression
 - posterior fossa craniotomy with microsurgical exploration of the root entry zone, displacement of the vessel impinging on the nerve with placement of a non-absorbable Teflon felt

Common Medications

The following are guidelines ONLY; follow clinical judgment and up-to-date prescription recommendations in practice; dosages refer to adults unless otherwise specified

Table 17. Common Medications

Drug Name	Dosing Schedule	Indications	Side Effects	Common Interactions	Contraindications	Comments
lorazepam (Ativan®)	4 mg IV over 2 minutes, q10-15 minutes (do not exceed 8 mg/12hr)	Status epilepticus	Drowsiness, sedation	Other CNS depressants, digoxin (increases digoxin levels)		Start phenytoin loading simultaneously
carbamazepine (Tegretol®)	Trigeminal neuralgia (tic douloureux): 100 mg PO bid, increase by 200 mg/day up to a maximum of 1,200 mg/day 200 mg tid Seizures: 200 mg PO bid, increase by 200 mg (inpatient: q3 days; outpatient: q7 days) until therapeutic level achieved (usual optimum dosage: 800-1,200 mg/day; range: 600-2,000 mg/day)	Trigeminal neuralgia Seizures	Worsening of seizures, heart failure, arrhythmias, AV block, aplastic anemia, agranulocytosis, thrombocytopenia, hepatitis, erythema multiforme, Stevens-Johnson syndrome	Lithium (increases lithium toxicity), MAOI Other meds may increase carbamazepine levels or have decreased effects	Hypersensitivity to TCAs, previous bone marrow suppression, MAOI in past 14 days	Monitor CBC (potential hematological toxicity)
phenytoin (Dilantin®)	Seizures: Loading dose: 18 mg/kg slow IV or 300-600 mg PO/day divided bid/tid Maintenance: 200-500 mg IV/day (max. rate: <40-50 mg/min or 300 mg PO q4h); average maintenance dose: 300 mg/day PO Status epilepticus: 200 mg IV over 30 minutes (~20 mg/kg; if not taking regularly), or 500 mg IV over 10 minutes (if already on phenytoin)	Seizures Status epilepticus	Thrombocytopenia, leukopenia, agranulocytosis, pancytopenia, toxic hepatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis	Other meds may increase phenytoin levels and toxicity or have decreased effects	Bradycardias, heart block	Important to give over time to prevent causing a cardiac arrest
dexamethasone (Decadron®)	Loading dose: 10-20 mg IV; Maintenance: 4-6 mg IV/day divided qid (may be PO)	Cerebral edema (e.g. secondary to tumour, head injury, pseudotumour cerebri) Preoperative preparation for patients with increased ICP secondary to brain neoplasms	Pseudotumour cerebri, seizures, heart failure, arrhythmias, thromboembolism, pancreatitis, acute adrenal insufficiency; avoid abrupt withdrawal	Aminoglutethimide, antidiabetics, ASA, NSAIDs, barbituates, phenytoin, rifampin, cardiac glycosides, cyclosporine, ephedrine, oral anticoagulants, potassium-depleting drugs, salicylates, skin-testing antigens, toxoids, vaccines	Systemic fungal infections, immunosuppressive dose with live virus vaccines	No longer used in acute spinal cord injury
mannitol	1-1.5 g/kg IV rapid infusion (350 mL of 20% solution) followed by 0.25 g/kg IV q6h	Raised ICP	Seizures, heart failure	Lithium (increases excretion of lithium)	Anuria, severe pulmonary congestion, frank pulmonary edema, severe heart failure, severe dehydration, metabolic edema, progressive renal disease or dysfunction, active intracranial bleeding except during craniotomy	Effect occurs in 1-5 mins, maximal at 20-60 mins Often alternated with furosemide 10-20 mg IV q6h Indwelling urinary catheter to measure ins and outs
nimodipine (Nimotop®)	60 mg PO/NG q4h x 21 days started within 96 hours of SAH	Vasospasm in SAH	Decreased blood pressure, tachycardia, dyspnea	Antihypertensives (may increase hypotensive effects), CCB (may increase effects), cimetidine (increases nimodipine bioavailability)	None known	Causes vasodilation Only calcium channel blocker (CCB) that crosses BBB (blood brain barrier) Use half the normal dose for liver failure; monitor BP always

References

- Ahn NU, Ahn UM, Nallamshetty L, et al. Cauda equina syndrome in ankylosing spondylitis (the CES-AS syndrome): meta-analysis of outcomes after medical and surgical treatments. *Journal of Spinal Disorders* 2001;14:427-33.
- Aids to the examination of the peripheral nervous system. London, UK: Balliere Tindall, 1986.
- Al-Shahi R, Warlow CP. Interventions for treating brain arteriovenous malformations in adults. *The Cochrane Library* 2004;Volume 2.
- Barker FG 2nd, Ogilvy CS. Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: a metaanalysis. *Journal of Neurosurgery* 1996;84:405-14.
- Barnett H, Taylor W, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *NEJM* 1998;339:1415-25.
- Bracken MB, Shepard MJ, Holford TR, et al. Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow up. Results of the third National Acute Spinal Cord Injury randomized controlled trial. *Journal of Neurosurgery* 1998;89:699-706.
- Crossman AR, Neary D. *Neuroanatomy: an illustrated colour text*. Toronto, ON: Churchill Livingstone, 1998.
- Edlow J, Caplan L. Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. *NEJM*. 2000;342(1):29-36.
- Executive Committee for the Asymptomatic Carotid Atherosclerosis Study (ACAS).
- Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;273:1421-28.
- Fehlings MG, Tator CH. An evidence-based review of surgical decompression for acute spinal cord injury: rationale, indications, and timing based on experimental and clinical studies. *J. Neurosurg.* 1999;91(1 Suppl):1-11.
- Fitzgerald MJT. *Neuroanatomy: basic and clinical* (3rd edition). Philadelphia: WB Saunders, 1997.
- Goetz CG, Pappert EJ. *Textbook of clinical neurology* (1st edition). Toronto, ON: WB Saunders, 1999.
- Greenberg MS. *Handbook of neurosurgery* (5th edition). New York: Thieme, 2001.
- Guy M, McKhann, Guy Mckhann II, Neil Kitchen. *Clinical Neurology and Neurosurgery*. Theme Medical Publishers. 2003
- Kun, LE. *Brain Tumours: Challenges and Directions*. Pediatric Clinics of North America. 1997; Vol 44(4):907-17.
- Lindsay KW, Bone I. *Neurology and neurosurgery illustrated*. New York: Churchill Livingstone, 2004.
- MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;363:1491-502.
- Nieuwenhuys R, Voogd J, van Huijzen C. *The human central nervous system* (3rd edition). New York: Springer-Verlag, 1988.
- Nursing 2004 Drug Handbook (24th edition). New York, NY: Springhouse Lippincott Williams & Wilkins, 2004.
- Ogilvy CS, Stieg PE, Awad I, et al. Recommendations for the management of intracranial arteriovenous malformations. *Circulation* 2001;103:2644-57.
- Portenoy RK, Lipton RB, Foley KM. Back pain in the cancer patient: An algorithm for evaluation and management. *Neurology*. 37:134-8, 1987.
- Porter PJ, Willinsky RA, Harper W, et al. Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. *Journal of Neurosurgery* 1997;87:190-7.
- Saal JS, Saal JA, Yurth EF. Nonoperative management of herniated cervical intervertebral disc with radiculopathy. *Spine*. 21(16):1877-83, 1996.
- Shapiro S. Medical realities of cauda equina syndrome secondary to lumbar disc herniation. *Spine*. 25(3):348-51; discussion 352, 2000.
- Shemie S, Doig C, Dickens B, et al. Severe brain injury to neurological determination of Death: Canadian forum recommendations. *CMAJ* 2006; 174(6): S1-30.
- Short DJ, El Masry WS, Jones PW. High dose methylprednisolone in the management of acute spinal cord injury – a systematic review from a clinical perspective. *Spinal Cord* 2000;38:273-86.
- Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. *Lancet Neurol*. 2008 Jun;7(6):525-37.
- Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *Journal of Neurosurgery* 1986;65:476-83.
- The North American Symptomatic Carotid Endarterectomy Trial (NASCET). Beneficial effects of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *NEJM* 1991;325:445-53.

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Basic Anatomy Review

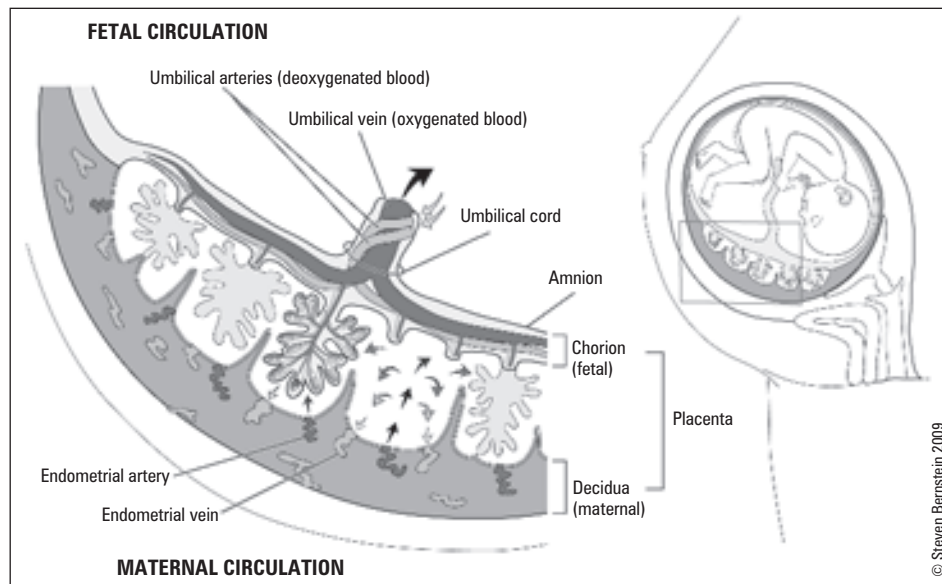


Figure 1. Placental Blood Flow



Umbilical Vessels

Always check the umbilical cord for 2 arteries and 1 vein: about 1/3 of babies with a single uterine artery will have another anomaly.

Placenta

- site of fetal nutritive, respiratory, and excretory function
- discoid mass composed of fetal (chorion frondosum) and maternal (decidua basalis) tissues divided by fissures into cotyledons (lobules) on the uterine side
- produces hormones such as progesterone, placental lactogen, estrogen, relaxin, beta-hCG and IGFs
- poor implantation can lead to spontaneous abortion
- abnormal location, implantation, or detachment can lead to antepartum hemorrhage (see *Antepartum Hemorrhage*, OB23)

Pregnancy



Diagnosis of Pregnancy

History

- obstetrical and gynecological history
- obtain the year, location, mode of delivery, duration of labour, sex, gestational age, birth weight and complications of every pregnancy; organize into **GTPAL** format:
 - Gravidity (G)
 - ♦ **G**: total number of pregnancies of any gestation
 - ♦ includes current pregnancy, abortions, ectopic pregnancies, and hydatidiform moles (multiple gestation = one pregnancy)
 - Parity (TPAL)
 - ♦ **T**: number of term infants delivered (>37 weeks)
 - ♦ **P**: number of premature infants delivered (20 to 37 weeks)
 - ♦ **A**: number of abortions (loss of intrauterine pregnancy prior to viability of fetus <20 weeks and/or <500 g fetal weight)
 - induced (therapeutic) and spontaneous (miscarriage)
 - ♦ **L**: number of living children
- symptoms: amenorrhea, nausea and/or vomiting, breast tenderness, urinary frequency, fatigue

Physical Signs

- Goodell's sign: softening of the cervix (4-6 weeks)
- Chadwick's sign: bluish discolouration of the cervix and vagina due to pelvic vasculature engorgement (6 weeks)
- Hegar's sign: softening of the cervical isthmus (6-8 weeks)
- uterine enlargement



Trimesters

- T1 (first trimester): 0-12 wks
- T2 (second trimester): 12-28 wks
- T3 (third trimester): 28-40 wks
- Normal pregnancy term: 37-42 wks



Physical Signs of Pregnancy

CHUG

- Chadwick's sign
- Hegar's sign
- Uterine enlargement
- Goodell's sign

Investigations

- **beta-hCG:** peptide hormone composed of alpha and beta subunits produced by placental trophoblastic cells – maintains the corpus luteum during pregnancy
 - positive in serum 9 days post-conception, positive in urine 28 days after first day of last menstrual period (LMP)
 - plasma levels double every 1-2 days, peak at 8-10 weeks, then fall to a plateau until delivery
 - ♦ levels less than expected by dates suggest: ectopic pregnancy, abortion, or inaccurate dates
 - ♦ levels higher than expected suggest: multiple gestation, molar pregnancy, trisomy 21, or inaccurate dates
- **U/S**
 - transvaginal
 - ♦ 5 weeks: gestational sac visible (beta-hCG $\geq 1,200$ -1,500 mIU/mL)
 - ♦ 6 weeks: fetal pole seen
 - ♦ 7-8 weeks: fetal heart tones visible
 - transabdominal
 - ♦ 6-8 weeks: intrauterine pregnancy visible (beta-hCG $\geq 6,500$ mIU/mL)



Beta-hCG Rule of 10s

10 IU at time of missed menses
100,000 IU at 10 weeks (peak)
10,000 IU at term

Maternal Physiology



Table 1. Physiologic Changes During Pregnancy

Skin	Increased pigmentation of perineum and areola, chloasma (pigmentation changes under eyes and on bridge of nose), linea nigra (midline abdominal pigmentation) Other: spider angiomas, palmar erythema due to increased estrogen, striae gravidarum due to connective tissue changes
Cardiovascular	Hyperdynamic circulation Increased CO, HR and blood volume Decreased BP due to decreased PVR Enlarging uterus compresses IVC and pelvic veins Decreased venous return leads to risk of hypotension Increased venous pressure leads to risk of varicose veins, hemorrhoids, leg edema
Hematologic	Hemodilution causes physiologic anemia and apparent decrease in hemoglobin and hematocrit Increased leukocyte count but impaired function leads to improvement in autoimmune diseases Gestational thrombocytopenia: mild (platelets $> 70,000/\mu\text{L}$) and asymptomatic, normalizes within 2-12 weeks following delivery Hypercoagulable state: increased risk of DVT and PE but also decreased bleeding at delivery Influence of beta-hCG resets osmostat leading to non-pathological hyponatremia
Respiratory	Increased incidence of nasal congestion and epistaxis Increased O_2 consumption to meet increased metabolic requirements Elevated diaphragm i.e. patient appears more "barrel-chested" Increased minute ventilation leads to decreased CO_2 resulting in mild respiratory alkalosis that helps CO_2 diffuse across the placenta from fetal to maternal circulation No change in VC and FEV_1 Decreased TLC, FRC, and RV
Gastrointestinal	GERD due to increased intra-abdominal pressure and progesterone (causing decreased sphincter tone and delayed gastric emptying) Increased gallstones due to progesterone causing increased gallbladder stasis Constipation and hemorrhoids due to progesterone causing decreased GI motility Atypical appendicitis presentation due to upward displacement of appendix (e.g. RUQ pain)
Genitourinary	Increased urinary frequency due to increased total urinary output Increased incidence of UTI and pyelonephritis due to urinary stasis (see <i>Urinary Tract Infection</i> , OB18) Glycosuria that can be physiologic, must test for gestational diabetes mellitus (GDM) Ureters and renal pelvis dilation ($R > L$) due to progesterone-induced smooth muscle relaxation and uterine enlargement Increased CO and thus increased GFR leads to decreased creatinine (normal in pregnancy 35-44 mmol/L), uric acid, and BUN
Neurologic	Increased incidence of carpal tunnel syndrome and Bell's palsy
Endocrine	Thyroid: moderate enlargement and increased basal metabolic rate Increased total thyroxine and thyroxine binding globulin (TBG) Free thyroxine index and TSH levels are normal Adrenal: maternal cortisol rises throughout pregnancy (total and free) Calcium: decreased total maternal Ca due to decreased albumin Free ionized Ca (i.e. active) proportion remains the same due to parathyroid hormone (PTH), results in: increased bone resorption and gut absorption, increased bone turnover (but no loss of bone density due to estrogen inhibition)
Cervix	Goodell's sign, Chadwick's sign, Hegar's sign (see <i>Physical Signs of Pregnancy</i> , OB2)



Prenatal Care



Family doctors and midwives to consider OB consultation if:

- Insulin-dependent GDM
 - VBAC
 - HTN
 - Multiple gestation
 - Malpresentation
 - Active antepartum hemorrhage
 - PTL/PPROM
 - Failure to progress/descend
 - Induction/augmentation if high risk
 - Tears: 3rd or 4th degree
 - Retained placenta
- Note: Guidelines vary by institution.



Advise all women capable of becoming pregnant to supplement their diet with 0.4 mg/day of folic acid (CTFPHC Grade II-2-A Evidence).

- provided by obstetrician, family doctor, midwife, or multidisciplinary team (based on patient preference and risk factors)
- Antenatal Records (province specific)

Preconception Counselling

- 3-8 weeks gestational age (GA) is a critical period of organogenesis, so early preparation is vital
- **past medical history:** optimize medical illnesses and necessary medications prior to pregnancy (see *Medical Conditions in Pregnancy*, OB11, and *Drugs in Pregnancy*, OB52)
- **supplementation**
 - folic acid: encourage diet rich in folic acid and supplement 8-12 wks preconception to prevent neural tube defects (NTDs)
 - ♦ 0.4-1 mg daily in all women, 5 mg if previous NTD, anti-epileptic medications, diabetes mellitus or BMI >35 kg/m²) and continue for T1 of pregnancy
 - iron supplementation, prenatal vitamins
- **risk modification**
 - lifestyle: balanced nutrition and physical fitness
 - infection screening: rubella, HBsAg, VDRL, Pap smear, gonorrhea/chlamydia, HIV, toxoplasmosis, CMV, TB, varicella
 - genetic testing as appropriate for high risk groups (see *Prenatal Screening* section, Table 4, OB7); consider genetics referral in known carriers, recurrent pregnancy loss/stillbirth, family members with developmental delay or birth anomalies
 - social: alcohol, smoking, drug use, domestic violence
 - ♦ use Antenatal Psychosocial Health Assessment (ALPHA) form to screen for antenatal risk factors associated with poor postpartum family outcomes (woman abuse, child abuse, postpartum depression, marital dysfunction and increased physical illness)

Initial Prenatal Visit

- within 12 weeks of the first day of LMP or earlier if <20 or >35 years old
- fill out Antenatal Records

History

- gestational age by dates from the first day of the LMP
- if LMP unreliable, get a dating ultrasound (see below)
- estimated date of confinement (EDC) using Naegle's Rule:
 - 1st day of LMP + 7 days – 3 months
 - e.g. LMP = 1 Apr 2011, EDC = 8 Jan 2012 (modify if cycle >28 days by adding number of days >28)
- history of present pregnancy (e.g. bleeding, nausea, vomiting)
- history of all previous pregnancies: GTPAL, year, sex, weight, gestational age, mode of delivery, length of labour, complications
- past medical history, past gynecological history
- prescription and non-prescription medications
- family history: genetic disease, birth defects, multiple gestation
- social history: smoking, alcohol, drug use, domestic violence (use ALPHA form)

Physical Examination

- complete exam to obtain baseline
- BP and weight important for interpreting subsequent changes
- pelvic exam

Investigations

- bloodwork
 - CBC, blood group and type, Rh antibodies, infection screening as per preconception counselling
- urine R&M, C&S
 - screen for bacteriuria and proteinuria
- pelvic exam
 - Pap smear (unless done within last 6-12 mo), cervical culture for *N. gonorrhoeae* (GC) and *C. trachomatis*, bacterial vaginosis (BV) vaginal swab



Ask every woman about abuse – not just those whose situations raise suspicion of abuse AND ask as early as possible in pregnancy. Be careful not to congratulate women on pregnancy, as many are unplanned and may be unwanted.



Tests for HIV, prenatal and genetic screening are voluntary and require proper counseling and informed consent before proceeding.

Counselling

- exercise
 - under physician guidance
 - absolute contraindications
 - ♦ ruptured membranes, preterm labour, hypertensive disorders of pregnancy, incompetent cervix, IUGR, multiple gestation (>3), placenta previa after 28th week, persistent 2nd or 3rd trimester bleeding, uncontrolled type I diabetes, thyroid disease, or other serious cardiovascular, respiratory or systemic disorder
 - relative contraindications
 - ♦ previous spontaneous abortion, previous preterm birth, mild/moderate cardiovascular or respiratory disorder, anemia ($Hb \leq 100$ g/L), malnutrition or eating disorder, twin pregnancy after 28th week, other significant medical conditions
- nutrition
 - Canada's Food Guide to Healthy Eating suggests:
 - ♦ 3-4 servings of milk products daily (greater if multiple gestation)
 - ♦ a daily caloric increase of ~100 cal/d in the 1st trimester, ~300 cal/d in the second and third trimesters and ~450 cal/d during lactation
 - daily multivitamin should be continued in the 2nd trimester for women who do not consume an adequate diet; otherwise routine vitamin supplementation is not necessary (avoid excess vitamin A)
 - see *Drug and Food Safety in Pregnancy*, OB52
- nutrients important during pregnancy
 - folate: 0.4-5 mg per day
 - ♦ supports maternal increase in blood volume, growth of maternal and fetal tissue, decreases incidence of neural tube defects
 - ♦ foods rich in folic acid include: spinach, lentils, chick peas, asparagus, broccoli, peas, Brussels sprouts, corn and oranges
 - calcium: 1200-1500 mg per day
 - ♦ maintains integrity of maternal bones, skeletal development of fetus, breast milk production
 - vitamin D: 400 IU
 - ♦ promotes calcium absorption
 - iron: 0.8 mg/d in T1, 4-5 mg/d in T2 and >6 mg/d in T3
 - ♦ supports maternal increase in blood cell mass, supports fetal and placental tissue
 - ♦ required amounts exceed normal body stores and typical intake, and therefore need supplemental iron
 - ♦ iron is the only known nutrient for which requirements during pregnancy cannot be met by diet alone (see *Iron Deficiency Anemia*, OB11)
 - essential fatty acids (EFA) – supports fetal neural and visual development
 - ♦ contained in vegetable oils, margarines, peanuts, fatty fish
- weight gain: optimal gain depends on pre-pregnancy weight (varies from 6.8-18.2 kg)
- work: strenuous work, extended hours and shift work during pregnancy may be associated with greater risk of low birth weight, prematurity, and spontaneous abortion
- travel: not harmful, but stress related to travel may be associated with preterm labour
 - air travel is acceptable in second trimester but discouraged after 36 weeks
- sexual intercourse: may continue except in patients at risk for abortion, preterm labour, or placenta previa; breast stimulation may induce uterine activity and is discouraged in high-risk patients near term
- address social issues including physical or sexual abuse
- smoking: assist/encourage to reduce or quit smoking
- alcohol: encourage abstinence from alcohol during pregnancy
- genetic screening must be offered to all women (see *Prenatal Screening*, OB7 and *Chromosomal Screening*, OB9)



Risk Factors for Neural Tube Defects

GRIMM

- Genetics: family history of NTD (risk of having second child with NTD is increased to 2-5%), consanguinity, chromosomal (characteristic of trisomy 13, 18, and 21)
- Race: European Caucasians > than African Americans, 3-fold higher in Hispanics
- Insufficient vitamins: zinc and folate
- Maternal chronic disease (e.g. diabetes)
- Maternal use of anti-epileptic drugs

General population risk for NTD is 0.1%.



Expected Weight Gain

BMI (kg/m ²)	Weight (kg)
<19	12.7-18.2
19-25	11.3-15.9
>25	6.8-11.3

General Rule: 1-3.5 kg/week during T1, then 0.45 kg/week until delivery

Subsequent Prenatal Visits

Timing

- for uncomplicated pregnancies, q4-6 weeks until 28 weeks, q2 weeks from 28 to 36 weeks and weekly from 36 weeks until delivery

Assess at Every Visit

- record estimated GA
- history of present pregnancy: fetal movements, uterine bleeding, leaking, cramping
- physical exam: BP, weight gain, symphysis fundal height (SFH), Leopold's maneuvers (T3) for lie, position and presentation of fetus
- investigations: urinalysis for glucosuria, ketones, proteinuria; fetal heart tones starting at 12 weeks using Doppler U/S



Symphysis Fundal Height (SFH)

12 weeks:	Uterine fundus at pubic symphysis
20 weeks:	Fundus at umbilicus SFH should be within 2 cm of GA between 20 and 36 weeks
37 weeks:	Fundus at sternum



Small for dates:
Date miscalculation
IUGR
Fetal Demise
Oligohydramnios

Large for dates:
Date miscalculation
Multiple gestation
Polyhydramnios

Leopold's Maneuvers

- performed after 30-32 weeks gestation
- first maneuver: to determine which fetal part is lying furthest away from the pelvic inlet
- second maneuver: to determine the location of the fetal back
- third maneuver (Pawlick's Grip): to determine which fetal part is lying above the pelvic inlet
- fourth maneuver: to locate the fetal brow

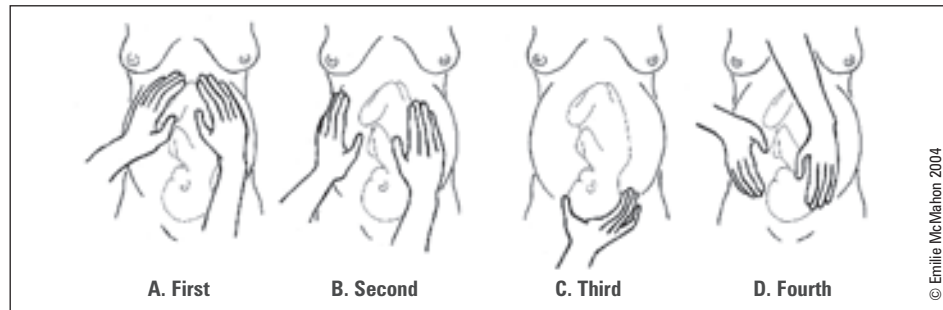


Figure 2. Leopold's Maneuvers (T3)

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Prenatal Fetal Monitoring



DDx of Decreased Fetal Movements

DASH

Death of fetus
Amniotic fluid decreased
Sleep cycle of fetus
Hunger/Thirst

Fetal Movements

- generally first noticed ("quickening") at 18-20 wks in primigravidas; can occur 1-2 wks earlier in multigravidas
- if mother is concerned about decreased movement: mother chooses a time when fetus is normally active to count movements (usually recommended after 28 wks)
 - if <6 movements in 2 hours, try drinking juice, eating, changing position or moving to a quiet room and count for another 2 hours
 - if decreased movement persists, notify MD



NON-STRESS TEST (NST)

Definition

- fetal heart rate (FHR) tracing ≥ 20 minutes using an external Doppler to assess FHR and its relationship to fetal movement (see *Fetal Monitoring in Labour* section, OB33)

Indication

- any suggestion of uteroplacental insufficiency or suspected fetal distress

Table 2. Classification of Antepartum Non-Stress Test

Parameter	Normal NST (Previously "Reactive")	Atypical NST (Previously "Non-Reactive")	Abnormal NST (Previously "Non-Reactive")
Baseline	110-160 bpm	100-110 bpm or > 160 bpm for < 30 min Rising baseline	Bradycardia < 100 bpm Tachycardia > 160 for > 30 min Erratic baseline
Variability	6-25 bpm (moderate) ≤ 5 (absent or minimal) for < 40 min	5 (absent or minimal) for 40-80 min 25 bpm for > 10 min	≤ 5 for 80 min Sinusoidal
Decelerations	None or occasional variable < 30 sec	Variable decelerations 30-60 sec duration	Variable decelerations > 60 sec Late deceleration(s)
Accelerations in Term Fetus	2 accelerations with acme of ≥ 15 bpm, lasting 15 sec over < 40 min of testing	2 accelerations with acme of ≥ 15 bpm, lasting 15 sec in 40-80 min	< 2 accelerations with acme of ≥ 15 bpm, lasting 15 sec in > 80 min
Accelerations in Preterm Fetus (< 32 weeks)	> 2 accelerations with acme of > 10 bpm, lasting 10 sec in < 40 min	< 2 accelerations with acme of > 10 bpm, lasting 10 sec in 40-80 min	< 2 accelerations with acme of > 10 bpm, lasting 10 sec in > 80 min
Action	FURTHER ASSESSMENT OPTIONAL , based on total clinical picture	FURTHER ASSESSMENT REQUIRED	URGENT ACTION REQUIRED An overall assessment of the situation and further investigation with U/S or BPP is required. Some situations will require delivery



Normal (Reassuring) NST: 2 accels,
 > 15 bpm from baseline, lasting > 15 s
in 20 min

Operating Characteristics

- false positive rate depends on duration; false negative rate = 0.2-0.3%

Interpretation

- normal (reassuring NST): at least 2 accelerations of FHR >15 bpm from the baseline lasting >15 seconds, in 20 minutes
- abnormal (non-reassuring NST): <2 accelerations of FHR in 40 minutes
 - if no observed accelerations or fetal movement in the first 20 minutes, stimulate fetus (fundal pressure, acoustic/vibratory stimulation) and continue monitoring for 30 minutes
 - if NST abnormal, then perform biophysical profile (BPP)

BIOPHYSICAL PROFILE (BPP)

Definition

- U/S assessment of the fetus \pm NST

Indications

- non-reassuring NST
- post-term pregnancy
- decreased fetal movement
- any other suggestion of fetal distress or uteroplacental insufficiency

Operating Characteristics

- false positive rate \leq 30%, false negative rate = 0.1%

Interpretation

- 8: perinatal mortality rate 1:1000; repeat BPP as clinically indicated
- 6: perinatal mortality 31:1000; repeat BPP in 24 hours
- 0-4: perinatal mortality rate 200:1000; deliver fetus if benefits of delivery outweigh risks

Table 3. Scoring of the Biophysical Profile

Parameter	Reassuring (2 points)	Non-Reassuring (0 points)
AFV*	Fluid pocket of 2 cm in 2 axes	Oligohydramnios
Breathing	At least one episode of breathing lasting at least 30 seconds	No breathing
Limb Movement	Three discrete movements	Two or less
Fetal Tone	At least one episode of limb extension followed by flexion	No movement

*Amniotic fluid volume (AFV) is a marker of chronic hypoxia, all other parameters indicate acute hypoxia



Reassuring BPP (8/8)

LAMB

Limb extension + flexion

AFV 2 cm x 2 cm

Movement (3 discrete)

Breathing (one episode x 30 s)

Prenatal Screening

- testing should only occur following counselling and with the informed consent of the patient

Table 4. High-Risk Population Screening Tests

Disease [Inheritance]	Population(s) at Risk	Screening Test(s)
Thalassemia [AR]	Mediterranean, South East Asian, Western Pacific , African, Middle Eastern, Caribbean, South American	CBC (MCV and MCH), Hb electrophoresis or HPLC
Sickle Cell [AR]	African, Caribbean , Mediterranean, Middle Eastern, Indian, South American	CBC (MCV and MCH), Hb electrophoresis or HPLC
Cystic Fibrosis (CF) [AR]	Mediterranean, Finnish, Caucasian, or FHx	CFTR gene DNA analysis
Tay Sachs Disease [AR]	Ashkenazi Jewish*, French Canadians, Cajun	Enzyme assay HEXA, or DNA analysis HEXA gene
Fragile X Syndrome [X-linked]	Family history – confirmed or suspected	DNA analysis: FMR-1 gene

AR = autosomal recessive; HPLC = high performance liquid chromatography; HEXA = hexosaminidase A

*If both partners are Ashkenazi Jewish, test for Canavan disease and Familial Dysautonomia (FD); if family history of a specific condition, look for carrier status: e.g. Gaucher, CF, Bloom syndrome, Niemann-Pick disease, etc. In all cases, if both partners positive, refer for genetic counselling.

Table 5. Gestation-Dependent Screening Investigations

Gestational Age (weeks)	Investigations
8-12	Dating U/S, initial Pap smear, chlamydia/gonorrhea cultures
10-12	Chorionic villus sampling (CVS)
11-14	First trimester screening (FTS) Integrated prenatal screening (IPS) Part 1
11-14	Nuchal translucency U/S
15-16 to term	Amniocentesis
15-18	Integrated prenatal screening (IPS) Part 2
16-18	Maternal serum screen (or MSAFP only for patients who did FTS earlier)
18-20 to term	Fetal movements (quickening)
18-20	U/S for dates, fetal growth and anatomy assessment
24-28	50 g oral glucose challenge test (OGCT)
28	Repeat CBC RhIG for all Rh negative women
36	Rh antibody screen if indicated Group B <i>Streptococcus</i> (GBS) Screen
6 weeks postpartum	Discuss contraception, menses, breastfeeding, depression, mental health, support Physical exam: breast exam, pelvic exam including Pap smear


Routine T2 U/S at 18-22 weeks, helps determine:

- Number of fetuses
- GA (if no prior U/S)
- Location of placenta
- Fetal anomalies

ULTRASOUND SCREENING

- dating ultrasound best done between 8-12 weeks GA
 - measurement of crown-rump length (margin of error \pm 3 days)
 - change EDC to U/S date if >1 week discrepancy from EDC based on LMP
- nuchal translucency ultrasound (NTUS) at 11-14 weeks GA
 - measures the amount of fluid behind the neck of the fetus
 - early screen for serious congenital anomalies (Down syndrome)
 - NT measurement is necessary for the FTS and IPS Part 1
- fetal growth and anatomy ultrasound routinely done at 18-20 weeks GA (margin of error \pm 7 days) (see *Pediatrics*, P43 for congenital anomalies)
- earlier or subsequent ultrasounds performed when medically indicated

Table 6. Comparison of FTS, MSS and IPS

First Trimester Screen (FTS)	Maternal Serum Screen (MSS)	Integrated Prenatal Screen (IPS)
11-14 wks	15-18 wks	Nuchal translucency on 12 wk U/S FTS at 11-14 wks MSS + inhibin A at 15-18 wks
Measures 1. Nuchal translucency on U/S 2. Beta-hCG 3. Pregnancy-associated plasma protein A (PAPP-A)	Measures 1. Maternal serum alpha-fetoprotein (MSAFP) 2. Beta-hCG 3. Unconjugated estrogen (estriol or uE3)	
Risk estimate for 1. Down syndrome (Trisomy 21): increased NT, increased beta-hCG, decreased PAPP-A	Risk estimate for 1. Open neural tube defect (oNTD): increased MSAFP (sensitivity 80-90%) 2. Trisomy 21: decreased MSAFP, increased beta-hCG, decreased uE3 (sensitivity 65%) 3. Trisomy 18: decreased MSAFP, decreased beta-hCG, decreased uE3 (sensitivity 80%)	Risk estimate for oNTD, Trisomy 21, Trisomy 18 Sensitivity ~85-90% 2% false positive rate Patients with positive screen should be offered U/S and/or amniocentesis
Note: does not measure risk of oNTD and should be combined with MSAFP at 16 weeks Useful where patient wants results within the first trimester More accurate estimate of Down syndrome risk than MSS, sensitivity ~85% (when combined with age) 5% false positive rate Patients with positive screen should be offered CVS or amniocentesis	Only offered alone if patient missed the time window for IPS or FTS 8% baseline false positive rate for t21, lower for oNTD and t18 Patients with positive screen should be offered U/S or amniocentesis	

Note: In twins, FTS, MSS and IPS are not applicable; screen with NT for chromosomal abnormalities and MSAFP for oNTDs.

CHROMOSOMAL SCREENING

Indications

- maternal age >35 (increased risk of chromosomal anomalies)
- risk factors in current pregnancy:
 - teratogen exposure
 - abnormal U/S
 - abnormal prenatal screen (FTS, MSS or IPS)
- past history/family history of:
 - previous pregnancy with chromosomal anomaly or genetic disease
 - either parent a known carrier of a genetic disorder or balanced translocation
 - family history of chromosomal anomaly, genetic disorder, birth defect, or undiagnosed mental retardation
 - consanguinity
 - three or more spontaneous abortions

AMNIOCENTESIS

- U/S-guided transabdominal extraction of amniotic fluid

Indications

- identification of genetic anomalies (15-16 weeks gestation) as per indications above
- assessment of fetal lung maturity (T3) via the L/S ratio (lecithin:sphingomyelin)
 - if >2:1, respiratory distress syndrome (RDS) is less likely to occur
- assessment of amniotic fluid bilirubin concentration in Rh-isoimmunized pregnancies

Advantages

- also screens for oNTD (acetylcholinesterase and amniotic AFP) – 96% accurate
- in women >35 years, the risk of chromosomal anomaly (1/180) is greater than the risk of miscarriage from the procedure
- more accurate genetic testing than CVS

Disadvantages

- 0.5% risk of spontaneous abortion and risk of fetal limb injury
- results take 14-28 days

CHORIONIC VILLUS SAMPLING (CVS)

- biopsy of fetal-derived chorion using a trans-abdominal needle or trans-cervical catheter at 10-12 weeks

Advantages

- enables pregnancy to be terminated earlier than with amniocentesis
- rapid karyotyping and biochemical assay within 48 hours, including FISH analysis
- high sensitivity and specificity

Disadvantages

- 1-2% risk of spontaneous abortion and risk of fetal limb injury
- does not screen for open neural tube defects
- 1-2% incidence of genetic mosaicism → false negative results

ISOIMMUNIZATION SCREENING

Definition

- isoimmunization: antibodies (Ab) produced against a specific RBC antigen (Ag) as a result of antigenic stimulation with RBC of another individual

Etiology

- maternal-fetal circulation normally separated by placental barrier, but sensitization can occur and can affect the current pregnancy, or more commonly, future pregnancies
- in pregnancy, anti-Rh Ab produced by a sensitized Rh-negative mother can lead to fetal hemolytic anemia
- overall risk of isoimmunization of an Rh-negative mother with an Rh-positive ABO-compatible infant is 16% (2% antepartum, 7% within 6 months of delivery, and 7% in the second pregnancy)
- sensitization routes
 - incompatible blood transfusions
 - previous fetal-maternal transplacental hemorrhage (e.g. ectopic pregnancy)
 - invasive procedures in pregnancy (e.g. prenatal diagnosis, cerclage, D&C)
 - any type of abortion
 - labour and delivery



DDx of Increased MSAFP

- Incorrect GA
- >1 fetus (e.g. twins)
- Fetal demise
- oNTD
- Abdominal wall defects (e.g. omphalocele)



DDx of Decreased MSAFP

- Incorrect GA
- Gestational trophoblastic neoplasia
- Missed abortion
- Chromosomal anomalies
- Maternal diabetes



L/S Ratio (Lecithin:Sphingomyelin Ratio)

Lecithin levels increase rapidly after 35 weeks gestation, whereas sphingomyelin levels remain relatively constant. The L/S ratio is a measure of fetal lung maturity – less than 2:1 indicates pulmonary immaturity. Presence of blood or meconium in the amniotic fluid can affect the ratio.



Compared to CVS, amniocentesis has a higher accuracy of prenatal cytogenetic diagnosis (99.8% vs. 97.5%) and lower risk of spontaneous abortion (0.5% vs. 1-2%).

**Rh Antibody Titre**

A positive titre ($\geq 1:16$) indicates an increased risk of fetal hemolytic anemia.

Investigations

- routine screening at first visit for blood group, Rh status, and antibodies are measured by the indirect Coombs test
- if Rh positive with antibodies present, the severity of fetal anemia is determined primarily by antibody concentration
 - Ab titres $<1:16$ considered benign
 - Ab titres $\geq 1:16$ necessitates amniocentesis to determine severity of fetal anemia (which correlates with the amount of biliary pigment in amniotic fluid from 27 wks onward)
- Kleihauer-Betke test used to determine extent of fetomaternal hemorrhage
 - fetal red blood cells identified on a slide treated with citrate phosphate buffer because adult hemoglobin elutes through cell membrane in presence of acid more readily
- detailed U/S for hydrops fetalis

Prophylaxis

- exogenous Rh IgG (Rhogam® or WinRho®) binds to Rh antigens of fetal cells and prevents them from contacting maternal immune system
- Rhogam® (300 µg) given to all Rh negative women in the following scenarios:
 - routinely at 28 weeks GA (provides protection for ~12 wks)
 - within 72 hours of the birth of an Rh positive fetus
 - with a positive Kleihauer-Betke test
 - with any invasive procedure in pregnancy (CVS, amniocentesis)
 - in ectopic pregnancy
 - with miscarriage or therapeutic abortion (only 50 µg required)
 - with an antepartum hemorrhage
- if Rh negative and Ab screen positive, follow mother with serial monthly Ab titres throughout pregnancy ± serial amniocentesis as needed (Rhogam® has no benefit)

Investigations

- bilirubin is measured by serial amniocentesis to assess the severity of hemolysis
- cordocentesis for fetal Hb: should be used cautiously (not first line)

Treatment

- falling biliary pigment warrants no intervention (usually indicative of either unaffected or mildly affected fetus)
- intrauterine transfusion of O-negative pRBCs may be required for severely affected fetus or early delivery of the fetus for exchange transfusion

Complications

- anti-Rh IgG can cross the placenta and cause fetal RBC hemolysis resulting in fetal anemia, CHF, edema, ascites
- severe cases can lead to fetal hydrops (edema in at least two fetal compartments due to fetal heart failure secondary to anemia) or erythroblastosis fetalis (moderate to severe immune-mediated hemolytic anemia)

GROUP B STREPTOCOCCUS (GBS) SCREEN**Epidemiology**

- 15-40% vaginal carrier rate

Risk Factors (for neonatal disease)

- GBS bacteriuria during current pregnancy even if treated
- previous infant with invasive GBS infection
- preterm labour <37 weeks
- ruptured membranes >18 hours before delivery
- intrapartum maternal temperature $\geq 38^\circ\text{C}$
- positive GBS screen during current pregnancy

Clinical Features

- not harmful to mother
- risk of vertical transmission (neonatal sepsis, meningitis or pneumonia)

Investigations

- offer screening to all women at 35-37 weeks with vaginal and anorectal swabs for C&S

Treatment

- treatment of maternal GBS at delivery decreases neonatal morbidity and mortality
- indications for antibiotic prophylaxis: positive GBS screen or GBS status unknown and one of the risk factors (see above)
- antibiotics for GBS prophylaxis
 - penicillin G 5 million units IV then 2.5 million units IV q4h until delivery
 - penicillin allergic but not at risk for anaphylaxis – cefazolin 2 g IV then 1 g q8h
 - penicillin allergic and at risk for anaphylaxis – clindamycin 900 mg IV q8h or erythromycin 500 mg IV q6h
- if fever, broad spectrum antibiotic coverage is advised

Screening vs. Risk-based Approach for GBS Prevention in Newborns

NEJM 2002; 347:233-9

Study: Large retrospective cohort study comparing the effectiveness of screening and risk-based approaches in preventing early-onset GBS disease (within 7 days of birth).

Patients: Stratified random sample of 629,912 live births in areas where there was active surveillance for GBS infection, the records for 5144 live births (screened group: $n=2628$; risk-based group: $n=2515$) were randomly selected to be reviewed, including all births where newborns had early-onset disease ($n=312$).

Intervention: Screening approach (routine screening with cultures for GBS between 35-37 wks GA and offering intrapartum antibiotic prophylaxis to carriers) vs. risk-based approach (offering intrapartum antibiotic prophylaxis to women presenting at time of labour with clinical risk factors for GBS transmission – fever, prolonged ROM, preterm delivery, etc.).

Main outcome: Early-onset GBS disease

Results: Infants of women in the screened group had a significantly lower risk of early-onset disease compared to those in the risk-based group ($RR=0.46$; 95% $CI=0.36$ to 0.60). The greatest risk factors for early-onset disease were (a) intrapartum fever ($RR=5.99$; 95% $CI=4.28$ - 8.38) and (b) history of a previous child with GBS disease ($RR=3.79$, 95% $CI=1.30$ - 11.11).

Conclusion: Routine screening for GBS during pregnancy is more effective for preventing GBS disease in newborns than the risk-based approach.

Termination of Pregnancy

Definition

- active termination of a pregnancy before fetal viability (usually <500 g or 20 weeks GA)

Indications

- inability to carry a pregnancy to term due to medical or social reasons (including patient preference)

Management

- medical**
 - <9 weeks: methotrexate + misoprostol
 - >12 weeks: prostaglandins (intra- or extra-amniotically or IM) or misoprostol
- surgical**
 - <12-16 weeks: dilatation + vacuum aspiration ± curettage
 - >16 weeks: dilatation and evacuation, early induction of labour
 - common complications: pain or discomfort
 - less common complications: hemorrhage, perforation of uterus, laceration of cervix, risk of infertility, infection/endometritis, Asherman's syndrome (adhesions within the endometrial cavity causing amenorrhea/infertility), retained products of conception
- counselling**
 - supportive services
 - future contraception plans
 - ensure follow-up



CMA policy (1988)

"Induced abortion should be uniformly available to all women in Canada" and "there should be no delay in the provision of abortion services".



Terminations are generally done until the stage of viability (~23.5 weeks), although this varies depending on the provider.



Induced Abortion Statistics

- Rate per 1,000 women (all ages): 13.7
- Rate per 1,000 women (age 20-24): 27.7
- Ratio of induced abortions per 100 live births (all ages): 28.3
- Ratio of induced abortions per 100 live births (age 20-24): 54.9
- 31.4% of all abortion services are accessed by women aged 20-24

Adapted from Statistics Canada, 2005, *Induced Abortion Statistics*, 82-223-XWE, page 16 of 32.

Medical Conditions in Pregnancy

Iron and Folate Deficiency Anemia

Table 7. Iron Deficiency and Folate Deficiency Anemia

	Iron Deficiency Anemia	Folate Deficiency Anemia
Etiology	Nutritional: inadequate intake Decreased iron absorption (malabsorption syndrome, antacid use) Increased iron losses (vaginal bleeding, other source of bleeding) Increased iron requirement (fetal growth, multiple gestation)	Nutritional: decreased intake Non-nutritional factors: multiple gestation, drugs (phenytoin, methotrexate), chronic hemolytic anemia, malabsorption entities (celiac sprue) Takes approximately 18 weeks of a folate-deficient diet to produce anemia
Epidemiology	Responsible for 80% of causes of non-physiologic anemia during pregnancy	Incidence varies from 0.5-25% depending on region, population, diet
Clinical Features	Same as in non-pregnant states Non-specific symptoms: pallor, fatigue, palpitations, tachycardia, dyspnea Severe anemia: angular stomatitis, glossitis	Non-specific symptoms: anorexia, nausea, vomiting, diarrhea, depression, pallor, UTI, sore mouth or tongue
Investigations	Serum iron, serum ferritin, blood smear – do not include total iron binding capacity (TIBC) since it is increased during normal pregnancy	RBC, serum folate, blood smear
Management	Prevention: 150 mg ferrous sulfate OD, 300 mg ferrous gluconate OD or 30 mg of ferrous iron OD for all pregnant women in T2 and T3 If anemic: 1 g ferrous sulfate OD (180 mg elemental Fe)	Prevention: 0.4-1 mg folic acid PO daily for 1-3 months preconceptually and throughout T1, or 5 mg folic acid per day with past history of oNTD, diabetes or anti-epileptic medication use
Complications	Maternal: angina, CHF, infection, slower recuperation, preterm labour Fetal: decreased oxygen carrying capacity leading to fetal distress, IUGR, low birth weight and hydrops	Maternal: decreased blood volume, nausea, vomiting, anorexia Fetal: neural tube defects in T1, low birth weight, prematurity
Notes	Mother needs 1 g of elemental iron per fetus; this amount exceeds normal stores + dietary intake Iron requirements increase during pregnancy due to fetal/placental growth (500 mg), increased maternal RBC mass (500 mg) and losses (200 mg) – more needed for multiple gestations	Minimum daily requirement is 0.4 mg Most often associated with iron deficiency anemia Folic acid is necessary for closure of neural tube during early fetal development (by day 28 of gestation)



Diabetes Mellitus (DM)

Classification of Diabetes Mellitus

- Type 1 and Type 2 DM (see Endocrinology, E6)
- gestational diabetes mellitus (GDM): onset of diabetes mellitus during pregnancy

Etiology

- Type 1 and Type 2 DM
- GDM: usually around 24-28 weeks GA, anti-insulin factors produced by placenta and high maternal cortisol levels create increased peripheral insulin resistance → higher fasting glucose → leading to GDM and/or exacerbating pre-existing DM

Epidemiology

- 2-4% of pregnancies are complicated by DM

MANAGEMENT

A. TYPE I AND TYPE 2 DM

Preconception

- pre-plan and refer to high-risk clinic
- optimize glycemic control
- counsel patient re: potential risks and complications
- evaluate for diabetic retinopathy, neuropathy, coronary artery disease

Pregnancy

- if already on medication, generally switch to insulin therapy
 - continuing glyburide or metformin controversial
 - teratogenicity unknown for other oral anti-hyperglycemics
- tight glycemic control
 - diet management first line therapy
 - post-prandial blood glucose values seem to be the most effective at determining the likelihood of macrosomia or other adverse pregnancy outcomes
 - aim for Fasting Plasma Glucose (PG) ≤ 5.3 mmol/L (95 mg/dL), 1-hour post prandial PG ≤ 7.8 mmol/L (140 mg/dL), 2-hour post prandial PG ≤ 6.7 mmol/L (120 mg/dL)
 - if blood glucose not well controlled, initiate insulin therapy
 - insulin dosage may need to be adjusted in T2 due to increased demand and increased insulin resistance
- monitor as for normal pregnancy plus initial 24-hr urine protein and creatinine clearance, retinal exam, HbA_{1C}
 - HbA_{1C}: $>140\%$ of pre-pregnancy value associated with increased risk of spontaneous abortion and congenital malformations
- increased fetal surveillance (BPP, NST)

Labour

- timing of delivery depends on fetal and maternal health and risk factors (i.e. must consider size of baby, lung maturity, maternal blood glucose and blood pressure control)
- can wait for spontaneous labour if blood glucose well-controlled and BPP normal
- induce by 40 weeks
- type of delivery
 - increased risk of cephalopelvic disproportion (CPD) and shoulder dystocia with babies $>4,000$ g (8.8 lbs)
 - elective C/S for predicted birthweight $>4,500$ g (9.9 lbs) (controversial)
- monitoring
 - during labour monitor blood glucose q1h with patient on insulin and dextrose drip
 - aim for blood glucose between 3.5 to 6.5 mmol/L to reduce the risk of neonatal hypoglycemia

Postpartum

- insulin requirements dramatically drop with expulsion of placenta (source of insulin antagonists)
- no insulin is required for 48-72 hours postpartum in most Type 1 DM
- monitor glucose q6h, restart insulin at two-thirds of pre-pregnancy dosage when glucose >8 mmol/L

B. GESTATIONAL DIABETES MELLITUS

Screening + Diagnosis

- at 24-28 weeks GA
- pregnant females age >25 or age <25 years with >1 risk factor (see sidebar)
- 1-hour, 50 g Oral Glucose Challenge Test (OGCT): not fasting
 - PG <7.8 mmol/L (140 mg/dL) = no GDM
 - PG ≥7.8-10.3 mmol/L = further investigation with OGTT
 - PG ≥10.3 mmol/L (185 mg/dL) = GDM
- 2-hour, 75 g Oral Glucose Tolerance Test (OGTT): fasting
 - FPG ≥5.3 mmol/L (95 mg/dL)
 - PG 1-hour ≥10.6 mmol/L (190 mg/dL)
 - PG 2-hour ≥8.9 mmol/L (160 mg/dL)
 - ♦ 2/3 of the above = GDM
 - ♦ 1/3 of the above = impaired glucose tolerance (IGT)



Risk factors for GDM:

- Age >25
- Obesity
- Ethnicity (Aboriginal, Hispanic, Asian, African)
- FHx of DM
- Previous history of GDM
- Previous child with birthweight >4.0 kg

Management

- treat both GDM and IGT
- tight glycemic control optimal as in Type 1 and Type 2 DM
- monitoring and timing of delivery as for Type 1 and Type 2 DM
- stop insulin and diabetic diet postpartum
- follow-up with 2-hour, 75 g OGTT 6 weeks-6 months postpartum

Prognosis

- most maternal and fetal complications are related to hyperglycemia and its effects

Long Term Maternal Complications

- Type 1 and Type 2 DM: risk of progressive retinopathy and nephropathy
- GDM: 50% risk of developing Type 2 DM in next 20 years

Table 8. Complications of DM in Pregnancy

Maternal	Fetal
Obstetric <ul style="list-style-type: none"> • Hypertension/preeclampsia (especially if pre-existing nephropathy/proteinuria): insulin resistance is implicated in etiology of hypertension • Polyhydramnios: maternal hyperglycemia leads to fetal hyperglycemia, which leads to fetal polyuria (a major source of amniotic fluid) 	Growth Abnormalities <ul style="list-style-type: none"> • Macrosomia: maternal hyperglycemia leads to fetal hyperinsulinism resulting in accelerated anabolism • Intrauterine growth restriction (IUGR): due to placental vascular insufficiency
Diabetic Emergencies <ul style="list-style-type: none"> • Hypoglycemia • Ketoacidosis • Diabetic coma 	Delayed Organ Maturity <ul style="list-style-type: none"> • Fetal lung immaturity: hyperglycemia interferes with surfactant synthesis (respiratory distress syndrome)
End-organ involvement or deterioration (occur in DM1 and DM2, not in GDM) <ul style="list-style-type: none"> • Retinopathy • Nephropathy 	Congenital Anomalies (occur in DM1 and DM2, not in GDM) <ul style="list-style-type: none"> • 2-7x increased risk of cardiac (VSD), NTD, GU (cystic kidneys), GI (anal atresia), and MSK (sacral agenesis) anomalies due to hyperglycemia <i>Note:</i> Pregnancies complicated by GDM do not manifest an increased risk of congenital anomalies because GDM develops after the critical period of organogenesis (in T1)
Other <ul style="list-style-type: none"> • Pyelonephritis/UTI: glucosuria provides a culture medium for <i>E. coli</i> and other bacteria • Increased incidence of spontaneous abortion (in DM1 and DM2, not in GDM): related to pre-conception glycemic control 	Labour and Delivery <ul style="list-style-type: none"> • Preterm labour/prematurity: most commonly in patients with hypertension/preeclampsia. Preterm labour is associated with poor glycemic control but the exact mechanism is unknown • Increased incidence of stillbirth • Birth trauma: due to macrosomia, can lead to difficult vaginal delivery and shoulder dystocia
	Neonatal <ul style="list-style-type: none"> • Hypoglycemia: due to pancreatic hyperplasia and excess insulin secretion in the neonate • Hyperbilirubinemia and jaundice: due to prematurity and polycythemia • Hypocalcemia: exact pathophysiology not understood, may be related to functional hypoparathyroidism • Polycythemia: hyperglycemia stimulates fetal erythropoietin production



Hypertension in Pregnancy



Hypertension in Pregnancy

Adverse Maternal Conditions

- DBP >100 mmHg
- HELLP
- Cerebral haemorrhage
- Renal dysfunction – oliguria <500 ml/d
- Left ventricular failure, pulmonary edema
- Abruptio, DIC

Symptoms:

- Abdominal pain, nausea, vomiting
- Headaches, visual problems
- SOB, chest pain
- Eclampsia – convulsions

Adverse Fetal Conditions

- Intrauterine growth restriction
- Oligohydramnios
- Absent/reversed umbilical artery end diastolic flow
- **Can result in:**
 - Fetal disability and/or death

- hypertensive disorders are classified as:
 1. pre-existing (<20 wks GA) – 90% cases are essential, 10% are secondary
 2. gestational (≥20 wks GA)
- preeclampsia can occur with either pre-existing or gestational hypertension

1. PRE-EXISTING HYPERTENSION

A) WITHOUT PREECLAMPSIA

Definition

- HTN (>140/90) prior to 20 weeks GA [except in a gestational trophoblastic neoplasia (GTN)], persisting postpartum
- essential hypertension is associated with an increased risk of gestational HTN, abruptio placenta, IUGR and intrauterine fetal demise (IUFD)

Management

- alpha-methyldopa 250-500 mg PO tid/qid or labetalol 100-300 mg PO bid/tid
- no ACE inhibitors, diuretics or propranolol (teratogens)
- monitor progress with serial U/S

B) WITH PREECLAMPSIA

Definition

- pre-existing hypertension with new onset proteinuria or adverse conditions or resistant hypertension
- 2-7 fold increased likelihood of developing preeclampsia/eclampsia if pre-existing maternal hypertension
- occurs early, tends to be severe (often with IUGR) and to recur with subsequent pregnancies

Management

- stabilize and deliver: only “cure” is delivery of placenta, independent of gestational age (vaginal delivery preferred)
- increased maternal monitoring: hourly input and output, urine dip q12h and hourly neurological vitals
- increased fetal evaluation: continuous FHR monitoring
- anticonvulsant therapy
 - raises seizure threshold
 - Mg sulfate 4 g IV bolus over 20 min followed by maintenance of 2-4 g/hour
 - monitor for signs of Mg toxicity: depressed deep tendon reflexes, decreased RR, anuric, hypotonic, CNS or cardiac depression
 - antagonist to Mg sulfate: calcium gluconate (10%) 10 mL (1 g) IV over 2 minutes
- antihypertensive therapy
 - lowering BP decreases the risk of stroke
 - hydralazine 5-10 mg IV bolus over 5 minutes q15-30 minutes as necessary
 - labetalol 20-50 mg IV q10 minutes
 - 2nd line: nifedipine 10-20 mg PO q20-60 minutes
 - ACE-inhibitors are contraindicated
- postpartum management
 - risk of seizure highest in first 24 hours postpartum – continue Mg sulfate for 12-24 hours after delivery
 - vitals q1h
 - consider HELLP syndrome in toxic patients
 - most return to a normotensive BP within 2 weeks

2. GESTATIONAL HYPERTENSION

Etiology

- imbalance of thromboxane (vasoconstrictor) and prostaglandin (vasodilator), arteriolar constriction, capillary damage, protein extravasation, and hemorrhage
- occurs after 20 weeks GA, except in patients with trophoblastic diseases (hydatidiform mole, hydrops, choriocarcinoma) when it occurs before 20 weeks GA



Preeclampsia Investigations

CBC	LDH
Liver enzymes	Albumin
INR and aPTT	Bilirubin
Cr	Urine (dip ± 24 hour collection)
Uric Acid	

Risk Factors

- maternal factors
 - primigravida (80-90% of gestational HTN)
 - first conception with a new partner
 - PMHx or FHx of gestational HTN
 - DM, chronic HTN, or renal insufficiency
 - antiphospholipid antibody syndrome (APLA)
 - extremes of maternal age (<18 or >35 years)
- fetal factors
 - IUGR or oligohydramnios, GTN, multiple gestation, fetal hydrops

Clinical Evaluation of Gestational Hypertension

- in general, clinical evaluation should include the mother and fetus
- evaluation of mother:
 - RUQ pain, headache and visual disturbances are potentially ominous symptoms requiring immediate assessment
 - central nervous system
 - ♦ presence and severity of headache
 - ♦ visual disturbances – blurring, scotomata
 - ♦ tremulousness, irritability, somnolence
 - ♦ hyperreflexia
 - hematologic
 - ♦ bleeding, petechiae
 - hepatic
 - ♦ RUQ or epigastric pain
 - ♦ severe nausea and vomiting
 - renal
 - ♦ urine output and colour
 - non-dependent edema (i.e. hands and face)
- evaluation of fetus:
 - fetal movement
 - fetal heart rate tracing – NST
 - ultrasound for growth
 - biophysical profile
 - Doppler flow studies

Laboratory Evaluation of Gestational Hypertension

- hemoglobin, platelets, blood film
- PTT, INR, fibrinogen, D-dimer – especially if surgery or regional anesthetics are planned
- ALT, AST, LDH, bilirubin
- proteinuria, creatinine, uric acid
- 24-hour urine collection for total protein and creatinine clearance

Complications

- maternal
 - hemorrhagic stroke (50% of deaths)
 - left ventricular failure/pulmonary edema
 - liver and renal dysfunction
 - abruptio placentae
 - seizure
 - DIC (release of placental thromboplastin → consumptive coagulopathy)
 - HELLP syndrome (see Table 9)
 - ♦ treat with FFP infusion or plasma exchange
- fetal (2° to placental insufficiency)
 - IUGR, prematurity, abruptio placentae, IUFD

A) WITHOUT PREECLAMPSIA**Management**

- bedrest in left lateral decubitus position, normal salt and protein intake
- avoid diuretics and antihypertensives
- monitor for progression
- if ≥37 weeks GA, consider induction of labour (see *Induction of Labour*, OB35)

B) WITH PREECLAMPSIA**Definition**

- gestational hypertension with new onset proteinuria or one or more adverse condition(s)

Management

- see *Pre-existing Hypertension with Preeclampsia*, OB14

3. SEVERE PREECLAMPSIA

- definition: preeclampsia before 34 weeks GA with:
 - heavy proteinuria (3-5 g/day) or
 - one or more adverse condition(s)

Management of Gestational Hypertension with Seizures

- ABC's
- seizure prevention and control

**Hyperemesis Gravidarum****Definition**

- intractable nausea and vomiting, usually presents in T1 then diminishes; occasionally persists throughout pregnancy
- affects ~1% of pregnancies

Etiology

- multifactorial with hormonal, immunologic and psychologic components
- rapidly rising beta-hCG ± estrogen levels may be implicated

Investigations

- rule out systemic causes: GI inflammation, pyelonephritis, thyrotoxicosis
- rule out obstetrical causes: multiple gestation, GTN, HELLP syndrome
- CBC, electrolytes, BUN, creatinine, LFTs, urinalysis
- ultrasound

Management

- if severe: admit to hospital, NPO initially then small frequent meals of appealing foods, correct hypovolemia, electrolyte disturbance and ketosis
- thiamine supplementation may be indicated
- TPN (if very severe) to reverse catabolic state
- non-pharmacological
 - rest
 - avoid triggers (e.g. certain odours)
 - acupressure at inner aspect of the wrists
 - ginger is effective but teratogenic effect unknown
- pharmacological options
 - Diclectin® (10 mg doxylamine succinate with vitamin B₆) can be started at 2 tablets qhs + 1 tablet qAM + 1 tablet qPM (i.e. afternoon); dosage can be increased up to 8 tablets per day
 - Gravol® can be safely used as an adjunct to Diclectin® (1 suppository bid or 25 mg PO qid)

Complications

- maternal
 - dehydration, electrolyte and acid-base disturbances
 - Mallory-Weiss tear
 - Wernicke's encephalopathy, if protracted course
 - death
- fetal: usually none, IUGR is 15x more common in women losing >5% of pre-pregnancy weight

Jaundice in Pregnancy**Epidemiology**

- affects 1 in 1500 pregnancies

Etiology

- viral hepatitis (most common)
- unique to pregnancy (see Table 9)
 - cholestatic jaundice of pregnancy
 - HELLP syndrome
 - hepatic rupture, hematoma and infarct
 - acute fatty liver of pregnancy (AFLP)
 - hyperemesis gravidarum (rarely causes hepatic dysfunction)
- pre-existing conditions, see Gastroenterology, Liver/Biliary Tract, G31, G44



HELLP Syndrome
 Hemolysis
 Elevated Liver enzymes
 Low Platelets

Table 9. Conditions Causing Jaundice in Pregnancy

	HELLP Syndrome	Cholestatic Jaundice of Pregnancy	Hepatic Infarct, Hematoma, and Rupture	Acute Fatty Liver of Pregnancy (AFLP)
Definition	Hemolysis, Elevated Liver enzymes, Low Platelets Pathogenesis unknown	Clinical syndrome characterized by intense pruritus that precedes jaundice by 7-14 days Pathogenesis unknown, may be due to increased sensitivity to high levels of estrogen or abnormal progesterational steroids	Rare consequence of preeclampsia, typically occurring in T3 Vasospasm-induced hepatic infarction can lead to hematoma formation; hematoma can lead to rupture	Form of hepatic failure with coagulopathy and encephalopathy characterized by microvesicular fatty infiltrates in liver parenchyma Pathogenesis unknown
Epidemiology	Affects 20% of women with severe preeclampsia Presents >27 weeks GA (11% sooner); up to 30% of cases present AFTER delivery and with no previous signs of hypertension	17-29 weeks GA High incidence in Chile and Scandinavia; rare in Asian and African populations		1 in 7000 deliveries 3 rd trimester (28-40 weeks GA) Maternal mortality as high as 75%; resolution of hepatic dysfunction with delivery or termination of pregnancy
Clinical Features	Epigastric, RUQ or chest pain, N/V, symptoms of preeclampsia (headache, blurred vision, thirst) \pm jaundice Atypical presentations: asymptomatic reduction in platelet count, "flu-like" symptoms	Intense pruritis (usually, worst on palms and soles of feet) \pm icterus (1-2 weeks later) Steatorrhea unusual	Hepatic rupture: RUQ abdominal pain, abdominal distention, nausea/vomiting, and hypertension, followed by shock	Acute nausea/vomiting, severe upper abdominal pain preceding jaundice Confusion Preeclampsia Pruritus Range in presentation: • Mild • Fulminant: GI bleeding, hepatic coma, renal failure and true hepatic failure (coagulopathy and encephalopathy)
Investigations	AST (70-663 U/L), total bilirubin slightly increased, low platelet count (7-99), elevated LDH \pm elevated D-dimers, tissue polypeptide antigen (TPA) and fibronectin, fragmented RBCs on smear Liver biopsy (rarely done): periportal hemorrhage and fibrin deposition with periportal necrosis; macro- and microvesicular fatty deposits (NOT pericentral as in AFLP)	ALT <500 IU, ALP and GGT markedly elevated (to levels consistent with moderate to severe cholestasis)	Hemoperitoneum (paracentesis, U/S, CT, MRI showing ruptured liver)	Elevated PTT and low serum fibrinogen AST > ALT Hypoglycemia Preeclampsia and HELLP features Liver biopsy to establish diagnosis: • Microvesicular fatty infiltrates of the central zone hepatocytes • Oil Red O stain on frozen tissue • Electron microscopy on glutaraldehyde fixed tissue If liver biopsy not possible, CT most useful
Management	Supportive care (in ICU) and prompt delivery	Ursodeoxycholic acid (20-25 mg/kg/day) Pruritus: cholestyramine Prophylactic vitamin K before delivery Consider induction of labour (see <i>Induction of Labour</i> , OB35)	Aggressive: rapid delivery and trauma surgery to repair liver	Early diagnosis with prompt delivery followed by maximal supportive care • ABCs, mechanical ventilation, transfusion of blood products • Hepatic encephalopathy treatment – lactulose, catharsis • Treat hypoglycemia
Notes	Complications: sepsis, multi-system organ failure, hepatic failure, DIC, death (rare)	Selenium may be protective against cholestasis Strong familial predisposition Correlates with oral contraceptive sensitivity	Complications include death (mother and fetus) if untreated	Recovery begins with delivery Persistent or increasing hyperbilirubinemia and complications: • Should not be interpreted as indications for liver transplantation • Aggressive supportive measures



Treat asymptomatic bacteriuria in pregnancy because of increased risk of progression to cystitis, pyelonephritis and probable increased risk of PRETERM LABOUR.



Urinary Tract Infection (UTI)

Etiology

- increased urinary stasis from mechanical and hormonal (progesterone) factors
- organisms include GBS as well as those that occur in non-pregnant women

Epidemiology

- most common medical complication of pregnancy
- asymptomatic bacteriuria in 2-7% of pregnant women depending on parity and socioeconomic factors
- *note:* asymptomatic bacteriuria should be treated in pregnancy

Clinical Features

- may be asymptomatic
- dysuria, urgency, and frequency in cystitis
- fever, flank pain, costovertebral angle tenderness in pyelonephritis

Investigations

- urinalysis, urine C&S
- VCUG, cystoscopy, and renal function tests in recurrent infections

Management

- uncomplicated UTI
 - first line: amoxicillin (250-500 mg PO q8h x 7 days)
 - alternatives: TMP-SMX (Septra®) or nitrofurantoin (avoid sulpha drugs during last 6 weeks of pregnancy due to displacement of bilirubin from albumin and increased kernicterus in the newborn)
 - follow with monthly urine cultures
- pyelonephritis
 - hospitalization and IV antibiotics

Prognosis

- complications if untreated: acute cystitis, pyelonephritis, and possible preterm premature rupture of membranes (PPROM)
- recurrence is common

Infections During Pregnancy



Table 10. Infections During Pregnancy

Infection	Agent	Source of Transmission	Greatest Transmission Risk to Fetus	Effects on Fetus	Effects on Mother	Diagnosis	Management
Chicken Pox	Varicella zoster virus (herpes family)	To mom: direct, respiratory, To baby: transplacental	13-30 weeks GA, and 5d pre- to 2d post-delivery	Congenital varicella syndrome (limb aplasia, chorioretinitis, cataracts, cutaneous scars, cortical atrophy, IUGR, hydrops), preterm labour (prematurity)	Fever, malaise, vesicular pruritic lesions	Clinical, \pm vesicle fluid culture, \pm serology	VZIG for mother if exposed, decreases congenital varicella syndrome Note: Do not administer vaccine during pregnancy (live attenuated)
*CMV	DNA virus (herpes family)	To mom: blood/organ transfusion, sexual contact To baby: transplacental, during delivery, breast milk	T1-T3	5-10% develop CNS involvement (mental retardation, cerebral calcification, hydrocephalus, microcephaly, deafness, chorioretinitis)	Asymptomatic or flu-like	Serologic screen; isolate virus from urine or secretion culture	No specific treatment; maintain good hygiene and avoid high risk situations
Erythema Infectiosum (Fifth Disease)	Parvovirus B19	To mom: respiratory, infected blood products To baby: transplacental	10-20 weeks GA	Spontaneous abortion (SA), stillbirth, hydrops in utero	Flu-like, rash, arthritis; often asymptomatic	Serology, viral PCR, maternal AFP; if IgM present, follow fetus with U/S for hydrops	If hydrops occurs, consider fetal transfusion
Hepatitis B	DNA virus	To mom: blood, saliva, semen, vaginal secretions To baby: transplacental, breast milk	T3 10% vertical transmission if asymptomatic HBsAg +ve; 85-90% if HBsAg and HBeAg +ve	Prematurity, low birth weight, neonatal death	Fever, N/V, fatigue, jaundice, elevated liver enzymes	Serologic screening for all pregnancies	Rx neonate with HBIG and vaccine (at birth, 1, 6 mos); 90% effective
*Herpes Simplex Virus	DNA virus	To mom: intimate mucocutaneous contact, To baby: transplacental, during delivery	Delivery (if genital lesions present); less commonly in utero	Disseminated herpes (20%); CNS sequelae (35%); self-limited infection	Painful vesicular lesions	Clinical diagnosis	Acyclovir for symptomatic women, suppressive therapy at 36 wks controversial C/S if active genital lesions, even if remote from vulva
HIV	RNA retrovirus	To mom: blood, semen, vaginal secretions To baby: in utero, during delivery, breast milk	1/3 in utero, 1/3 at delivery, 1/3 breastfeeding	IUGR, preterm labour, premature rupture of membranes	See <u>Infectious Diseases</u> ID29	Serology, viral PCR All pregnant women are offered screening	Triple antiretroviral therapy decreases transmission to <1% Elective C/S: no previous antiviral Rx or monotherapy only, viral load unknown or >500 RNA copies/ml, unknown prenatal care, patient request
*Rubella	ssRNA togavirus	To mom: respiratory droplets (highly contagious) To baby: transplacental	T1	SA or congenital rubella syndrome (hearing loss, cataracts, CV lesions, MR, IUGR, hepatitis, CNS defects, osseous changes)	Rash (50%), fever, posterior auricular or occipital lymphadenopathy, arthralgia	Serologic testing; all pregnant women screened (immune if titre >1:16); infection if IgM present or >4x increase in IgG	No specific treatment; offer vaccine following pregnancy Do not administer during pregnancy (live attenuated)
Syphilis	Spirochete (<i>Treponema pallidum</i>)	To mom: sexual contact To baby: transplacental	T1-T3	Risk of PTL, multisystem involvement, fetal death	See <u>Infectious Diseases</u> ID26	VDRL screening for all pregnancies; if positive, requires confirmatory testing	Pen G 2.4 M U IM 1 dose if early syphilis 3 doses if late syphilis monitor VDRL monthly if Pen G allergic: consider desensitization before treatment
*Toxoplasmosis	Protozoa (<i>Toxoplasma gondii</i>)	To mom: raw meat, unpasteurized goat's milk, cat feces/urine To baby: transplacental	T3 (but most severe if infected in T1); only concern if primary infection during pregnancy	Congenital toxoplasmosis (chorioretinitis, hydrocephaly, intracranial calcification, MR, microcephaly) NB: 75% initially asymptomatic at birth	Majority subclinical; may have flu-like symptoms	IgM and IgG serology; PCR of amniotic fluid	Self-limiting in mother; spiramycin decreases fetal morbidity but not rate of transmission

* Indicates TORCH infection



Venous Thromboembolism (VTE)

Epidemiology

- incidence 0.5-3/1,000 pregnancies occurring with approximately equal frequency in all three trimesters and postpartum

Risk Factors

- previous VTE, age >35, obesity, infection, bedrest/immobility, shock/dehydration, thrombophilias (congenital and acquired, see [Hematology](#))

Table 11. Risk Factors for VTE Specific to Pregnancy

Hypercoagulability	Stasis	Endothelial
Increased factors: II, V, VII, VIII, IX, X, XII, fibrinogen Increased platelet aggregation Decreased protein S, tPA, factors XI, XIII Increased resistance to activated protein C Antithrombin can be normal or reduced	Increased venous distensibility Decreased venous tone 50% decrease in venous flow in lower extremity by T3 Uterus is mechanical impediment to venous return	Vascular damage at delivery (C/S or SVD) Uterine instrumentation Peripartum pelvic surgery

Clinical Features

- most DVTs occur in the iliofemoral or calf veins with a predilection for the left leg
- signs of a pulmonary embolism are non-specific (as in non-pregnant women)
- unexplained spontaneous fetal loss

Investigations

- duplex venous Doppler sonography for DVT
- CXR and V/Q scan for PE
- due to hypercoagulability, the normal scale for D-dimer levels must be adjusted (controversial)

Management

- before initiating treatment, obtain a baseline CBC, including platelets, and aPTT
- warfarin is contraindicated during pregnancy due to its potential teratogenic effects
- unfractionated heparin
 - bolus of 5000 IU followed by an infusion of ~30 000 IU/24 hours
 - measure aPTT six hours after the bolus
 - maintain aPTT at a therapeutic level (1.5-2 times normal)
 - repeat q24h once therapeutic
 - heparin-induced thrombocytopenia (HIT) uncommon (3%) but serious complication
- compression stockings
- poor evidence to support a recommendation for or against avoidance of prolonged sitting
- VTE prophylaxis:
 - women on long-term anticoagulation: full therapeutic anticoagulation throughout pregnancy and for 6-12 weeks postpartum
 - women with a non-active PMHx of VTE: unfractionated heparin regimens suggested
- routine VTE prophylaxis:
 - insufficient evidence in pregnancy to recommend routine use of LMWH
 - current prophylaxis regimens for acquired thrombophilias (e.g. APLA syndrome) include low dose aspirin in conjunction with prophylactic heparin



Virchow's Triad for VTE

- Hypercoagulable state
- Stasis
- Endothelial damage



Bleeding in Pregnancy Definitions

- First Trimester Bleeding: vaginal bleeding within the first 12 weeks
- Second Trimester Bleeding: <20 weeks



Approach to the Patient with Bleeding in T1/T2

History

- Risk factors for ectopic pregnancy (previous ectopic pregnancies, history of STI/PID, IUD use, previous pelvic surgery, smoking)
- Previous SA
- Recent trauma
- Characteristics of the bleeding (including any tissue passed)
- Characteristics of the pain (cramping pain suggests SA)
- History of coagulopathy
- Gynecological/obstetric history
- Dizziness (significant blood loss, may be associated with ruptured ectopic)
- Fever (may be associated with septic abortion)

Physical

- Vitals (including orthostatic changes)
- Abdomen (SFH, tenderness, presence of contractions)
- Perineum (signs of trauma, genital lesions)
- Speculum exam (cervical os open or closed, presence of active bleeding/clots/tissue)
- Pelvic exam (uterine size, adnexal mass, uterine/adnexal tenderness)

Bleeding in Pregnancy

First and Second Trimester Bleeding

Differential Diagnosis

- physiologic bleeding: spotting, due to implantation of placenta – reassure and check serial beta-hCGs
- abortion (threatened, inevitable, incomplete, complete) (see Table 12)
- abnormal pregnancy (ectopic, molar) (see [Gynecology](#) for *Molar Pregnancy*)
- trauma (post-coital or after pelvic exam)
- genital lesion (e.g. cervical polyp, neoplasms)

Investigations

- beta-hCG (lower than expected for GA in spontaneous abortion, ectopic pregnancy)
- U/S (confirm intrauterine pregnancy and fetal viability)
- CBC
- group and screen

Treatment

- IV resuscitation for hemorrhagic shock
- treat the underlying cause

Spontaneous Abortions

- see *Termination of Pregnancy*, OB11 for therapeutic abortions

Table 12. Classifications of Spontaneous Abortions

Type	History	Clinical	Management (\pm Rhogam [®])
Threatened	Vaginal bleeding \pm cramping	Cervix closed and soft U/S shows viable fetus	Watch and wait <5% go on to abort
Inevitable	Increasing bleeding and cramps \pm rupture of membranes	Cervix closed until products start to expel, then external os opens	a) Watch and wait b) Misoprostol 400-800 ug PO/PV c) D&C \pm oxytocin
Incomplete	Extremely heavy bleeding and cramps \pm passage of tissue noticed	Cervix open	a) Watch and wait b) Misoprostol 400-800 ug PO/PV c) D&C \pm oxytocin
Complete	Bleeding and complete passage of sac and placenta	Cervix open	No D&C – expectant management
Missed	No bleeding (fetal death in utero)	Cervix closed U/S may show SGA	a) Watch and wait b) Misoprostol 400-800 ug PO/PV c) D&C \pm oxytocin
Recurrent	3+ consecutive spontaneous abortions		Evaluate mechanical, genetic, environmental and other risk factors
Septic	Contents of uterus infected – infrequent		D&C IV broad spectrum antibiotics

**Etiology of Recurrent Pregnancy Loss****MAKE ME**

Mechanical: uterine anomaly, cervical incompetence (T2)
Autoimmune: antiphospholipid antibody syndrome, lupus anticoagulant
Karyotype: both parents
Endocrine: hypothyroidism, diabetes mellitus
Maternal infection
Environment: smoking, alcohol, drugs, radiation

**Management of Abortions**

- Always rule out an ectopic
- Always check Rh; if negative, give Rhogam[®]
- Always ensure patient is hemodynamically stable

Ectopic Pregnancy

Definition

- embryo implants outside of the endometrial cavity

Epidemiology

- 1/100 pregnancies
- fourth leading cause of maternal mortality, leading cause of death in first trimester
- increase in incidence over the last 3 decades
- three commonest locations for ectopic pregnancy: ampullary (78%), isthmic (12%), fimbrial (5%)

Etiology

- 50% due to damage of fallopian tube cilia from PID
- intrinsic abnormality of the fertilized ovum
- conception late in cycle
- transmigration of fertilized ovum to contralateral tube

Risk Factors

- previous ectopic pregnancy
- demographics: older women, of African descent
- smoking
- endometriosis
- gynecologic:
 - IUD use – although decreased pregnancy rate, there is increased risk of ectopic if pregnancy occurs
 - history of PID (especially infection with *C. trachomatis*), salpingitis
 - infertility
 - clomiphene citrate (for induction of ovulation)
- previous procedures:
 - any surgery on fallopian tube (for previous ectopic, tubal ligation, etc.)
 - abdominal surgery for ruptured appendix, etc.
 - IVF pregnancies following ovulation induction (7% ectopic rate)
- structural:
 - uterine leiomyomas
 - adhesions
 - abnormal uterine anatomy (e.g. T-shaped uterus)

**Clinical Features of Ectopic Pregnancy: 4Ts and 1S**

- **Temperature** >38°C (20%)
- **Tenderness:** abdominal (90%) \pm rebound (45%)
- **Tenderness** on bimanual examination, cervical motion tenderness
- **Tissue:** palpable adnexal mass (50%) (half have contralateral mass due to lutein cyst)
- **Signs of pregnancy** (e.g. Chadwick's sign, Hegar's sign)



More than half of patients with ectopic pregnancy have no risk factors.

**DDx of Lower Abdominal Pain**

Urinary tract: UTI, kidney stones
 GI: diverticulitis, appendicitis
 Gynae: endometriosis, PID, fibroid (degenerating, infarcted, torsion), ovarian torsion, ovarian neoplasm, ovarian cyst, pregnancy-related

**If Ectopic Pregnancy Ruptures**

Acute abdomen with increasing pain
 Abdominal distention
 Shock

Investigations

- serial beta-hCG levels; normal doubling time with intrauterine pregnancy is 1.6-2.4 days in early pregnancy
 - rise of <20% of beta-hCG is 100% predictive of a nonviable pregnancy
 - prolonged doubling time, plateau or decreasing levels before 8 weeks implies nonviable gestation but does not provide information on location of implantation
- ultrasound
 - U/S is only definitive if fetal cardiac activity is detected in the tube or uterus
 - intrauterine sac should be visible when serum beta-hCG is
 - ♦ >1500 mIU/mL (transvaginal)
 - ♦ >6000 mIU/mL or 6 weeks gestational age (transabdominal)
 - specific finding on transvaginal U/S is a tubal ring
- culdocentesis (rarely done)
- laparoscopy (for definitive diagnosis)

Treatment

- goals of treatment: conservative (preserve tube if possible)
- surgical (laparoscopy)
 - linear salpingostomy if tube salvageable
 - salpingectomy if tube damaged or ectopic is ipsilateral recurrence
 - 15% risk of persistent trophoblast; must monitor beta-hCG titres weekly until they reach non-detectable levels
 - if patient is Rh negative give anti-D gamma globulin (Rhogam®)
 - may require laparotomy
- medical = methotrexate
 - use 50 mg/m² body surface area; given in a single IM dose
 - this is 1/5 to 1/6 chemotherapy dose, therefore minimal side effects (reversible hepatic dysfunction, diarrhea, gastritis, dermatitis)
 - follow beta-hCG levels weekly until beta-hCG is non-detectable
 - ♦ plateau or rising levels suggest persisting trophoblastic tissue (requires further treatment)
 - 67% success rate; up to 25% will require a 2nd dose
 - tubal patency following methotrexate treatment approaches 80%

Prognosis

- 9% of maternal deaths during pregnancy
- 40-60% of patients will become pregnant again after surgery
- 10-20% will have subsequent ectopic gestation

Interventions for Tubal Ectopic Pregnancy

Cochrane Database of Systematic Reviews 2007, Issue 1

Study: Cochrane Review of randomized controlled trials comparing treatments in women with tubal ectopic pregnancy.

Patients: Women with a diagnosis of tubal ectopic pregnancy.

Intervention: Surgery-salpingectomy/salpingostomy by open surgery or by laparoscopy, medical treatment, and expectant management.

Main outcome: Primary treatment success, defined as an uneventful decline in serum beta-hCG to undetectable levels by the initial treatment.

Results: Intramuscular MTX therapy and salpingostomy yielded similar treatment success rates (82-95% for MTX therapy vs. 80-92% for salpingostomy).

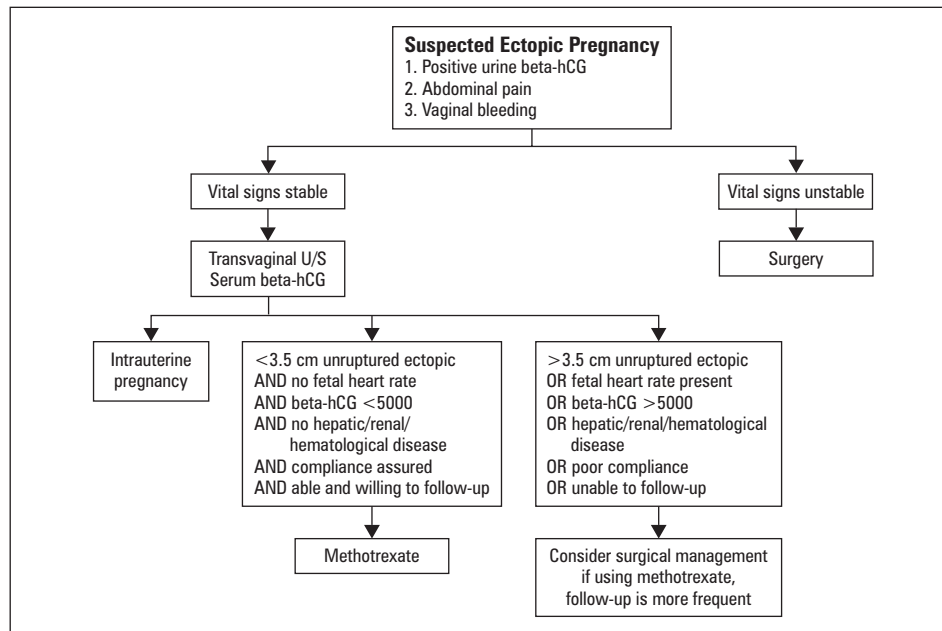


Figure 3. Algorithm for Suspected Ectopic Pregnancy

Antepartum Hemorrhage

Definition

- vaginal bleeding from 20 weeks to term

Differential Diagnosis

- bloody show (shedding of cervical mucous plug) – most common etiology in T3
- placenta previa
- abruptio placentae – most common pathological etiology in T3
- vasa previa
- marginal sinus bleeding
- cervical lesion (cervicitis, polyp, ectropion, cervical cancer)
- uterine rupture
- other: bleeding from bowel or bladder, placenta accreta, abnormal coagulation

Placenta Previa

Definition

- abnormal location of the placenta near, partially or completely over the cervical os

Etiology

- idiopathic

Epidemiology

- incidence = 0.5-0.8% of all pregnancies

Risk Factors

- history of placenta previa (4-8% recurrence risk)
- multiparity
- increased maternal age
- multiple gestation
- uterine tumour (e.g. fibroids) or other uterine anomalies
- uterine scar due to previous abortion, C/S, D&C, myomectomy

Clinical Features

• classification

- total: placenta completely covers the internal os
- partial: placenta partially covers the internal os
- marginal: within 2 cm of os but does not cover any part of os – causes potential risk of hemorrhage during cervical effacement and dilatation
- low lying (NOT a previa): placenta in lower segment but clear of os (can also bleed, but usually in labour)

• history

- PAINLESS** bright red vaginal bleeding (recurrent), may be minimized and cease spontaneously, but can become catastrophic
- mean onset of bleeding is 30 wks GA, but onset depends on degree of previa (total placenta previa bleed earlier, marginal bleed at onset of labour)

• physical exam

- uterus soft and non-tender
- presenting part high or displaced

• complications

- fetal
 - perinatal mortality low but still higher than with a normal pregnancy
 - prematurity (bleeding often dictates early C/S)
 - intrauterine hypoxia (acute or IUGR)
 - fetal malpresentation
 - PPROM
 - risk of fetal blood loss from placenta, especially if incised during C/S
- maternal
 - <1% maternal mortality
 - hemorrhage and hypovolemic shock, anemia, acute renal failure, pituitary necrosis (Sheehan syndrome)
 - placenta accreta – especially if previous uterine surgery, anterior placenta previa
 - hysterectomy



Do NOT perform a vaginal exam until placenta previa has been ruled out by U/S.



Levels of abnormal placental invasion:
Placenta Accreta – AT myometrium (most common)
Placenta Increta – INTO myometrium
Placenta Percreta – PASSES myometrium

Investigations

- ultrasound diagnosis (transabdominal ultrasound has 95% accuracy)
- due to development of lower uterine segment, 90-95% of previas diagnosed in T2 resolve by T3
- partial or total previas: repeat U/S at 30-32 weeks
- low-lying: repeat U/S not indicated unless recurrent bleeding

Management

- goal: keep pregnancy intrauterine until the risk of delivery < risk of not continuing pregnancy
- stabilize and monitor
 - maternal stabilization: large bore IV with hydration, O₂ for hypotensive patients
 - maternal monitoring: vitals, urine output, blood loss, bloodwork (hematocrit, CBC, INR/PTT, platelets, fibrinogen, FDP, type and cross match)
 - electronic fetal monitoring
 - U/S assessment: when fetal and maternal condition permit, determine fetal viability, gestational age and placental status/position
- Rhogam® if mother is Rh negative
 - Kleihauer-Betke test to determine extent of fetomaternal transfusion so that appropriate dose of Rhogam® can be given
- GA <37 weeks and minimal bleeding – expectant management
 - admit to hospital
 - limited physical activity, no douches, enemas, or sexual intercourse
 - consider corticosteroids for fetal lung maturity
 - delivery when fetus is mature or hemorrhage dictates
- GA ≥37 weeks, profuse bleeding or L/S ratio is >2:1 – deliver by C/S

**Kleihauer-Betke Test**

Quantifies fetal cells in the maternal circulation.

Abruptio Placentae

Definition

- premature separation of a normally implanted placenta after 20 weeks GA

Etiology

- most are idiopathic

Epidemiology

- incidence: 1-2% of all pregnancies

Risk Factors

- previous abruption (recurrence rate 5-16%)
- maternal hypertension (chronic or PIH in 50% of abruptions) or vascular disease
- cigarette smoking (>1 pack/day), excessive alcohol consumption, cocaine
- multiparity and/or maternal age >35 (felt to reflect parity)
- PPROM
- rapid decompression of a distended uterus (polyhydramnios, multiple gestation)
- uterine anomaly, fibroids
- trauma (e.g. motor vehicle collision, maternal battery)

Clinical Features

- **classification**
 - total (fetal death inevitable) vs. partial
 - external/revealed/apparent: blood dissects downward toward cervix
 - internal/concealed (20%): blood dissects upward toward fetus
 - most are mixed
- **presentation**
 - **PAINFUL** vaginal bleeding, uterine tenderness, uterine contractions
 - pain: sudden onset, constant, localized to lower back and uterus
 - ± fetal distress, fetal demise (15% present with demise), bloody amniotic fluid

Complications

- fetal complications: perinatal mortality 25-60%, prematurity, intrauterine hypoxia
- maternal complications: <1% maternal mortality, DIC (in 20% of abruptions), acute renal failure, anemia, hemorrhagic shock, pituitary necrosis (Sheehan syndrome), amniotic fluid embolus

Investigations

- clinical diagnosis: ultrasound not sensitive for abruption (sensitivity = 15%)



Abruptio placentae is the most common cause of DIC in pregnancy.

Table 13. Grades of Abruption Placentae

Grade	Uterine Irritability	Maternal Hemodynamics	Maternal Fibrinogen	FHR
Mild	Mild	Normal	Normal	Normal
Moderate	Moderate-severe ± tetany	BP with postural drop Increased HR	Decreased	Distress: decreased variability Late decelerations
Severe	Tetany	Decreased BP, decreased HR	Extremely decreased	Absent

Management

- maternal stabilization: large bore IV with hydration; O₂ for hypotensive patients
- maternal monitoring: vitals, urine output, blood loss, bloodwork (hematocrit, CBC, PTT/PT, platelets, fibrinogen, FDP, type and cross match)
- electronic fetal monitoring
- blood products on hand (red cells, platelets, cryoprecipitate) because of DIC risk
- Rhogam® if Rh negative
 - Kleihauer-Betke test may confirm abruption
- mild abruption:
 - GA <37 weeks: use serial Hct to assess concealed bleeding, deliver when fetus is mature or hemorrhage dictates
 - GA ≥37 weeks: stabilize and deliver
- moderate to severe abruption:
 - hydrate and restore blood loss and correct coagulation defect if present
 - vaginal delivery if no contraindication and no evidence of fetal or maternal distress OR fetal demise
 - C/S if live fetus and fetal or maternal distress develops with fluid/blood replacement, labour fails to progress or if vaginal delivery otherwise contraindicated

Table 14. Comparison of Abruption Placenta and Placenta Previa

Abruption Placenta	Placenta Previa
Abdominal PAIN and/or backache	PAINLESS
Uterine TENDERNESS	NO tenderness
INCREASED uterine tone	Uterus SOFT
Uterine IRRITABILITY/CONTRACTIONS	No uterine irritability/contractions
Usually NORMAL fetal presentation	Malpresentation and/or high presenting part
FHR may be ABSENT or abnormal tracing	FHR usually NORMAL
Shock and anemia OUT OF PROPORTION to apparent blood loss	Shock and anemia CORRESPOND to apparent blood loss
May have COAGULOPATHY	Coagulopathy very UNCOMMON initially

Vasa Previa**Definition**

- unprotected fetal vessels pass over the cervical os; associated with velamentous insertion of cord into membranes of placenta or succenturiate lobe

Epidemiology

- 1 in 5,000 deliveries – higher in twin pregnancies

Clinical Features

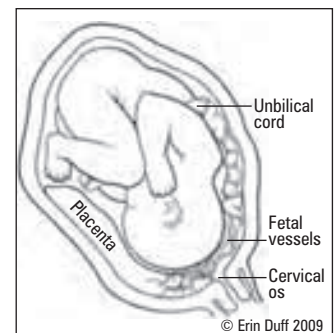
- PAINLESS** vaginal bleeding and fetal distress (tachy- to bradyarrhythmia)
- 50% perinatal mortality, increasing to 75% if membranes rupture (most infants die of exsanguination)

Investigations

- Apt test** (NaOH mixed with the blood) can be done immediately to determine if the source of bleeding is fetal (supernatant turns pink) or maternal (supernatant turns yellow)
- Wright stain** on blood smear and look for nucleated red blood cells (in cord, not maternal blood)

Management

- emergency C/S (since bleeding is from fetus, a small amount of blood loss can have catastrophic consequences)

**Figure 4. Vasa Previa**

Multiple Gestation

Epidemiology

- incidence of twins is 1/80 and triplets 1/6400 in North America
- 2/3 of twins are dizygotic (fraternal)
 - risk factors for dizygotic twins: IVF, increased maternal age, newly discontinued OCP, ethnicity (e.g. certain African regions)
- monozygous twinning occurs at a constant rate worldwide (1/250)
- determine zygosity by number of placentas, thickness of membranes, sex, blood type

Clinical Features

Table 15. Complications Associated with Multiple Gestation

Maternal	Utero-placental	Fetal
Hyperemesis gravidarum	Increased PROM/PTL	Prematurity*
GDM	Polyhydramnios	IUGR
Gestational HTN	Placenta previa	Malpresentation
Anemia	Placental abruption	Congenital anomalies
Increased physiological stress on all systems	PPH (uterine atony)	Twin-twin transfusion
Increased compressive symptoms	Umbilical cord prolapse	Increased perinatal morbidity and mortality
C/S	Cord anomalies (velamentous insertion, 2 vessel cord)	Twin interlocking (twin A breech, twin B vertex)
		Single fetal demise

*Most common cause of perinatal mortality in multiple gestation

Management

- U/S determination of chorionicity must be done within first trimester (ideally 8-12 weeks GA)
- increased antenatal surveillance
 - nonstress test (NST) weekly from 24 weeks GA
 - serial U/S q 2-3 weeks from 28 weeks GA to assess growth
 - Doppler flow studies weekly if discordant fetal growth
 - BPP as needed
- vaginal examinations in third trimester to check for cervical dilatation
- may attempt vaginal delivery if twin A presents as vertex, otherwise C/S (40-50% of all twin deliveries, 15% of cases have twin A delivered vaginally and twin B delivered by C/S)
- mode of delivery depends on fetal weight, GA, presentation

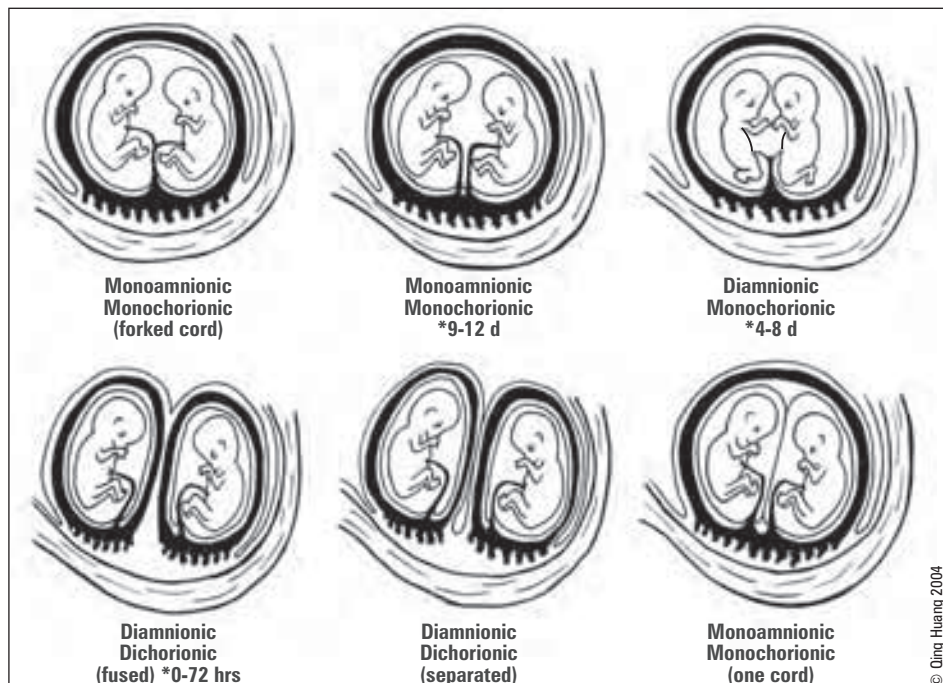


Figure 5. Classification of Twin Pregnancies

*Indicates time of cleavage



The P's of Multiple Gestation Complications

Increased rates of:

- Puking
- Pallor (anemia)
- Preeclampsia/PIH
- Pressure (compressive symptoms)
- PTL/PROM/PPROM
- Polyhydramnios
- Placenta previa/abruptio
- PPH/APH
- Prolonged labour
- Cord Prolapse
- Prematurity
- Mal Presentation
- Perinatal morbidity and mortality
- Parental distress
- Postpartum depression



Twin-Twin Transfusion Syndrome

Epidemiology

- 10% of monochorionic twins

Etiology

- arterial blood from donor twin passes through placenta into vein of recipient twin

Clinical Features

- donor twin: IUGR, hypovolemia, hypotension, anemia, oligohydramnios
- recipient twin: hypervolemia, hypertension, CHF, polycythemia, edema, polyhydramnios, kernicterus in neonatal period

Investigations

- detected by U/S screening, Doppler flow analysis

Management

- therapeutic serial amniocentesis to decompress polyhydramnios of recipient twin and decrease pressure in cavity and on placenta
- intrauterine blood transfusion to donor twin if necessary
- laparoscopic occlusion of placental vessels

Growth Discrepancies



Intrauterine Growth Restriction (IUGR)

Definition

- common definition: infant weight <10th percentile for GA
- other definitions: infant <2500 g, Ponderal Index: birth weight (gm)/crown-heel length (cm) x 100

Etiology/Risk Factors

- maternal causes
 - malnutrition, smoking, drug abuse, alcoholism, cyanotic heart disease, Type 1 DM, SLE, pulmonary insufficiency, previous IUGR
- maternal-fetal
 - any disease causing placental insufficiency
 - includes gestational HTN, chronic HTN, chronic renal insufficiency, gross placental morphological abnormalities (infarction, hemangiomas)
- fetal causes: TORCH infections, multiple gestation, congenital anomalies



TORCH

Toxoplasmosis

Others: e.g. syphilis

Rubella

CMV

HSV

- See Table 10, OB19

Clinical Features

- symmetric/Type I (20%) – occurs early in pregnancy
 - inadequate growth of head and body
 - **head:abdomen ratio** may be normal (>1 up to 32 weeks; =1 at 32-34 weeks; <1 after 34 weeks GA)
 - usually associated with congenital anomalies or TORCH infections
- asymmetric/Type II (80%) – occurs late in pregnancy
 - brain is spared, therefore head:abdomen ratio increased
 - usually associated with placental insufficiency
 - more favorable prognosis than Type I
- complications
 - prone to meconium aspiration, asphyxia, polycythemia, hypoglycemia, and mental retardation
 - greater risk of perinatal morbidity and mortality



Differential Diagnosis of Incorrect Uterine Size for Dates

- Inaccurate dates
- Maternal: diabetes mellitus
- Maternal-fetal: polyhydramnios, oligohydramnios
- Fetal: abnormal karyotype, IUGR, macrosomia, fetal anomaly, abnormal lie, multiple gestation

Investigations

- symphysis-fundus height (SFH) measurements at every antepartum visit
- if mother at high risk or SFH lags >2 cm behind GA:
 - anatomy U/S for biparietal diameter (BPD), head and abdomen circumference, femur length and fetal weight, amniotic fluid volume (decrease associated with IUGR)
 - \pm BPP
 - Doppler analysis of umbilical cord blood flow



Monitoring Fetal Growth with U/S
Done biweekly to show growth beyond the margin of error.

Management

- prevention via risk modification prior to pregnancy is ideal
- modify controllable factors: smoking, alcohol, nutrition and treat maternal illness
- bed rest in left lateral decubitus position (LLDP)
- serial BPP (monitor fetal growth) and determine cause of IUGR, if possible
- delivery when extrauterine existence is less dangerous than continued intrauterine existence (abnormal function tests, absent growth, severe oligohydramnios) especially if GA >34 weeks
- liberal use of C/S since IUGR fetus withstands labour poorly

Macrosomia

Definition

- infant weight >90th percentile for a particular GA or >4000 g

Etiology/Risk Factors

- maternal obesity, gestational diabetes mellitus, past history of macrosomic infant, prolonged gestation, multiparity

Clinical Features

- increased risk of perinatal mortality
- cephalopelvic disproportion (CPD) and birth injuries (shoulder dystocia, fetal bone fracture) more common
- complications of DM in labour (see *Medical Conditions in Pregnancy*, OB11)

Investigations

- serial SFH
- further investigations if mother at high risk or SFH >2 cm ahead of GA
- U/S predictors
 - polyhydramnios
 - third trimester abdominal circumference (AC) >1.5 cm/week
 - head circumference (HC)/AC ratio <10th percentile
 - femur length (FL)/AC ratio <20th percentile

Management

- prophylactic C/S is a reasonable option where estimated fetal weight (EFW) >5000 g in nondiabetic women and EFW >4500 g in diabetic women
 - no evidence that prophylactic C/S improves outcomes
- early induction of labour is not recommended for non-diabetic mothers
- risks and benefits of early induction (risk of C/S vs. risk of dystocia) must be weighed in diabetic mothers, as current research is unclear

Polyhydramnios/Oligohydramnios



Table 16. Polyhydramnios and Oligohydramnios

	Polyhydramnios	Oligohydramnios
Definition	Amniotic fluid volume (AFV) >2,000 cc at any stage in pregnancy U/S criteria: >8 x 8 cm (3.1 x 3.1 in) pocket of amniotic fluid	Amniotic fluid index of 5 cm (2 in) or less • Important sign of chronic placental insufficiency
Etiology	Idiopathic most common (40%) Maternal: • Type 1 DM: abnormalities of transchorionic flow Maternal-fetal: • Chorioangiomas • Multiple gestation • Fetal hydrops (increased erythroblastosis) Fetal: • Chromosomal anomaly (up to 2/3 of fetuses have severe polyhydramnios) • Respiratory: cystic adenomatoid malformed lung • CNS: anencephaly, hydrocephalus, meningocele • GI: tracheoesophageal fistula, duodenal atresia, facial clefts (interfere with swallowing)	Early onset oligohydramnios: • Decreased production: renal agenesis or dysplasia, urinary obstruction, posterior urethral valves (male), chronic hypoxemia and IUGR resulting in shunting away from the kidneys to ensure perfusion of the brain • Increased loss: prolonged amniotic fluid leak (although most often labour ensues) Late onset oligohydramnios: • Amniotic fluid normally decreases after 35 weeks • Common in post-term pregnancies • U/S Doppler studies (umbilical cord and uterine artery)
Epidemiology	Occur in 0.2 to 1.6% of all pregnancies	Occur in ~4.5% of all pregnancies Severe form in <0.7% Common in pregnancies >41 weeks (~12%)
Clinical Features and Complications	Pressure symptoms from overdistended uterus (dyspnea, edema, hydronephrosis) Uterus large for dates, difficulty palpating fetal parts and hearing fetal heart tones Cord prolapse, placental abruption, malpresentation, preterm labour, uterine dysfunction and PPH	Cord compression Increased risk of adverse fetal outcomes Early onset: • 15-25% have fetal anomalies • Amniotic fluid bands (T1) can lead to Potter's facies, limb deformities, abdominal wall defects Late onset: • Pulmonary hypoplasia • Marker for infants who may not tolerate labour well
Management	Determine underlying cause: • Screen for maternal disease/infection • Complete fetal U/S evaluation Depends on severity: • Mild to moderate cases require no treatment • If severe, hospitalize and consider therapeutic amniocentesis	Always warrants admission and investigation: • Rule out rupture of membranes (ROM) • Fetal monitoring (NST, CTG, BPP) • U/S Doppler studies (umbilical cord and uterine artery) Maternal hydration with oral or IV fluids to help increase amniotic fluid Vesicoamniotic shunt: if etiology is related to fetal obstructive uropathy; however, pulmonary function may not be restored with restoration of amniotic fluid Injection of fluid via amniocentesis will improve condition for ~1 wk – may be most helpful for visualizing any associated fetal anomalies Consider delivery if term Amnio-infusion may be considered during labour via intra-uterine catheter
Prognosis	Two to five-fold increase in risk of perinatal mortality	Poorer with early onset High mortality related to congenital malformations and pulmonary hypoplasia when diagnosed during T2



Normal Labour and Delivery

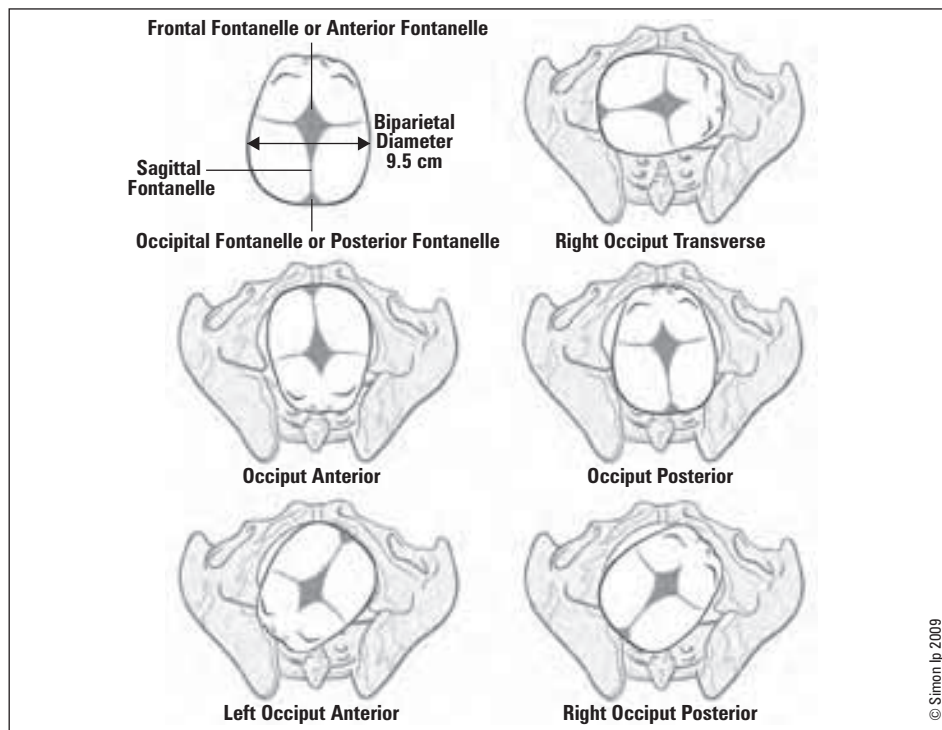


Figure 6. Fetal Positions

The Fetus



Presenting Parts include:

Occiput for vertex
Sacrum for breech
Mentum for face



Fetal lie: long axis of fetus compared to long axis of uterus

Fetal presentation: fetal part at pelvic outlet

Fetal position: position of presenting part relative to pelvis

- **fetal lie**
 - orientation of the long axis of the fetus with respect to the long axis of the uterus (longitudinal, transverse, oblique)
- **fetal presentation**
 - fetal part presenting at pelvic outlet
 - ♦ breech (complete, frank, footling) – see Figure 8, OB40
 - ♦ cephalic (vertex, face, asynclitic)
 - ♦ transverse (shoulder)
 - ♦ compound (fetal extremity prolapses along with presenting part)
 - all except vertex are considered malpresentations (see *High Risk Labour and Delivery*, OB37)
- **fetal position**
 - position of presenting part of the fetus relative to the maternal pelvis
 - ♦ occiput anterior (OA): most common presentation (“normal”) – left OA most common
 - ♦ occiput posterior (OP): most rotate spontaneously to OA; may cause prolonged second stage of labour
 - ♦ occiput transverse (OT): leads to arrest of dilatation
 - normally, fetal head enters maternal pelvis and engages in OT position
 - subsequently rotates to OA position (or OP in a small percentage of cases)
- **attitude**
 - flexion/extension of fetal head relative to shoulders
 - ♦ brow presentation: head partially extended (requires C/S)
 - ♦ face presentation: head fully extended
 - mentum posterior always requires C/S, mentum anterior will deliver vaginally
- **station**
 - position of presenting part relative to ischial spines – determined by vaginal exam
 - ♦ at ischial spines = station 0 = engaged
 - ♦ cm above (–5 → –1) or cm below (+1 → +5)

The Cervix

- dilatation: latent phase: 0-3 cm; active phase: 4-10 cm
- effacement: thinning of the cervix by percentage or length of cervix (cm)
- consistency: firm vs. soft
- position: posterior vs. anterior
- application: contact between the cervix and presenting part (i.e. well or poorly applied)
- see Bishop score (Table 20, OB36)

Definition of Labour

- true labour: regular, painful contractions of increasing intensity associated with progressive **dilatation** and **effacement** of cervix and **descent** of presenting part, or **progression of station**
 - preterm (>20 but <37 weeks GA)
 - term (37-42 weeks GA)
 - post-term (>42 weeks GA)
- false labour: Braxton-Hicks contractions
 - irregular contractions, with unchanged intensity and long intervals, occur throughout pregnancy and not associated with any dilatation, effacement or descent
 - often relieved by rest or sedation

Analgesic and Anaesthetic Techniques in Labour and Birth

- pain or anxiety leads to high endogenous catecholamines, which produce a direct inhibitory effect on uterine contractility

Non-pharmacologic Pain Relief Techniques

- reduction of painful stimuli
 - maternal movement, position change, counter-pressure, abdominal compression
- activation of peripheral sensory receptors
 - superficial heat and cold
 - immersion in water during labour
 - touch and massage, acupuncture and acupressure
 - transcutaneous electrical nerve stimulation (TENS)
 - intradermal injection of sterile water
 - aromatherapy
- enhancement of descending inhibitory pathways
 - attention focusing and distraction
 - hypnosis and self-hypnosis
 - music and audio analgesia
 - biofeedback

Pharmacologic Methods

- nitrous oxide (e.g. self-administered Entonox®)
- narcotics (usually combined with anti-emetic)
- pudental nerve block
- perineal infiltration with local anesthetic
- regional anaesthesia (epidural block)

Four Stages of Labour

First Stage of Labour

- latent phase
 - uterine contractions typically infrequent and irregular
 - slow cervical dilatation (usually to 3-4 cm) and effacement
- active phase
 - rapid cervical dilatation to full dilatation (nulliparous ~1.2 cm/h, multiparous ~1.5 cm/h)
 - phase of maximum slope on cervical dilatation curve (see Figure 9, OB43)
 - painful, regular contractions q2-3 min, lasting 45-60 seconds
 - contractions strongest at fundus, weakest at lower segment

Second Stage of Labour

- from full dilatation to delivery of the baby
- mother feels a desire to bear down and push with each contraction
- women may choose a comfortable position that enhances pushing efforts and delivery
 - upright (semi-sitting, squatting) and LLDP are supported in the literature
- progress measured by descent



Course of Normal Labour

Stage	Nulliparous	Multiparous
First	6-18 hours	2-10 hours
Second	30 min-3 hours	5-30 minutes
Third	5-30 minutes	5-30 minutes



Signs of Placental Separation

1. Gush of blood
2. Lengthening of cord
3. Uterus becomes globular
4. Fundus rises

Continuous Support for Women During Childbirth

Cochrane Database of Systematic Reviews 2007, Issue 3

Study: Systematic review of 16 RCTs from 11 countries, 13,391 women in labour.

Intervention: Continuous support during labour vs. usual care.

Outcome: Effects on mothers and their babies.

Results: Continuous intrapartum support increased likelihood of shorter labour, spontaneous vaginal birth, decrease in analgesia use, and a decrease in dissatisfaction with childbirth experience. Greatest benefit when provider is not a health care professional.

Third Stage of Labour

- separation and expulsion of the placenta
- can last up to 30 minutes before intervention indicated
- start oxytocin IV drip or give 10 U IM after delivery of anterior shoulder in anticipation of placental delivery; otherwise give after delivery of placenta
- routine oxytocin administration in third stage of labour can reduce the risk of PPH by >40%

Fourth Stage of Labour

- first postpartum hour
- monitor vital signs and bleeding
- repair lacerations
- ensure uterus is contracted (palpate uterus and monitor uterine bleeding)
- inspect placenta for completeness and umbilical cord for presence of 2 arteries and 1 vein
- 3rd and 4th stages of labour most dangerous to the mother (i.e. hemorrhage)

The Cardinal Movements of the Fetus During Delivery

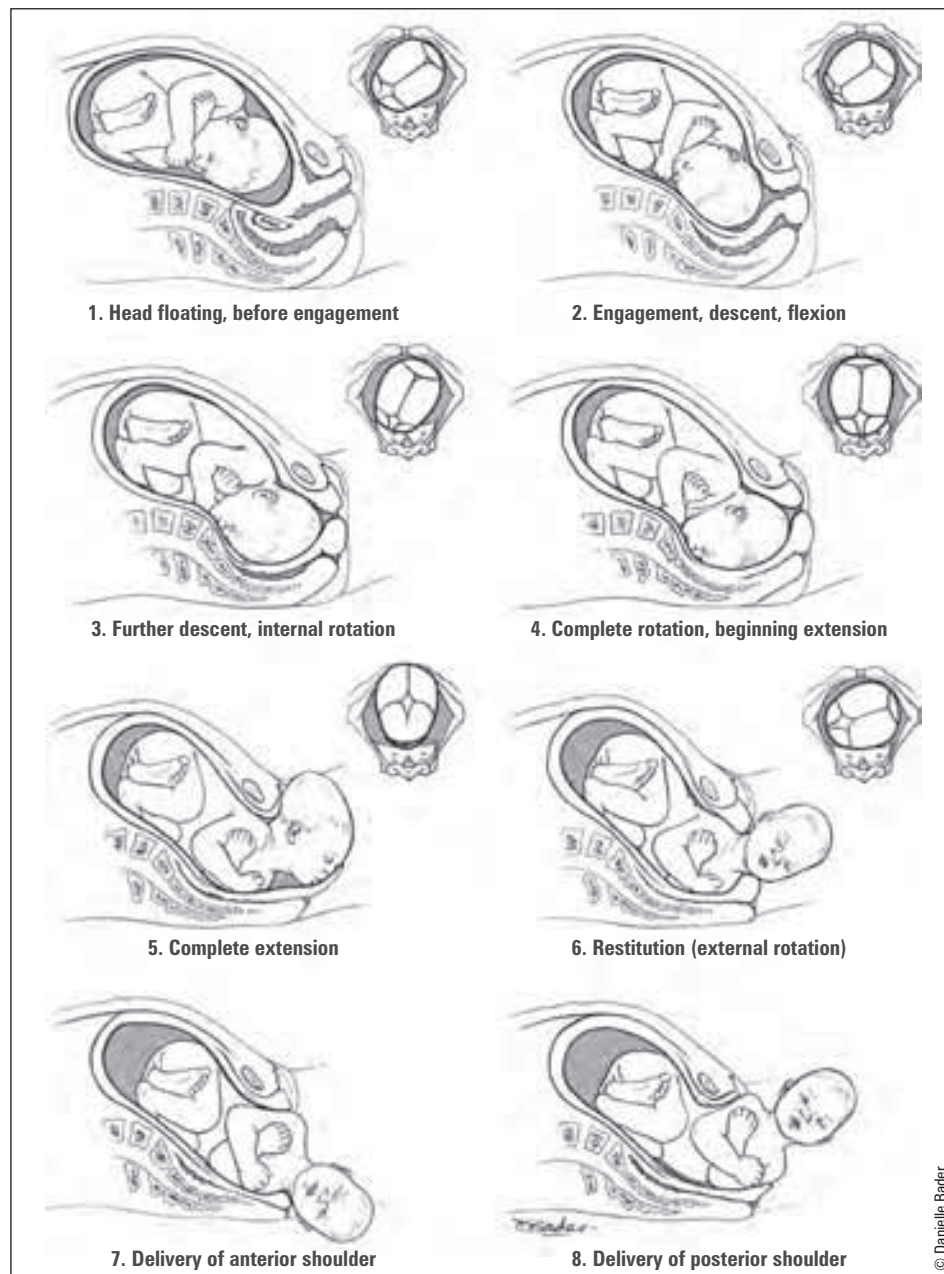


Figure 7. Cardinal Movements of Fetus During Delivery

Adapted from illustration in *Williams Obstetrics*, 19th Ed.

Fetal Monitoring in Labour

- see online **Fetal Heart Rate Tutorial**

Vaginal Exam

- membrane status
- cervical effacement (thinning), dilatation, consistency, position, application
- fetal presenting part, position, station
- bony pelvis size and shape
- monitor progress of labour at regular intervals and document in a partogram

Intrapartum Fetal Monitoring

- intermittent fetal auscultation with Doppler device q15-30 minutes for one minute in first stage active phase following a contraction, q5 minutes during second stage when pushing has begun
- continuous electronic FHR monitoring reserved for non-reassuring auscultation, prolonged labour, and labour which is induced or augmented
 - routine use of continuous electronic monitoring shown to lead to higher intervention rates and no improvement in outcome for the neonate
 - techniques for continuous monitoring include external (Doppler) vs. internal (fetal scalp electrode) monitoring
- fetal scalp sampling should be used in conjunction with electronic FHR monitoring and contraction monitoring (cardiotocometry – CTG) to resolve the interpretation of non-reassuring patterns

Electronic Fetal Heart Rate (FHR) Monitoring

- FHR measured by Doppler; contractions measured by tocometer
- described in terms of baseline FHR, variability (short term, long term) and periodicity (accelerations, decelerations)
- **Baseline FHR**
 - normal range is 110-160 bpm
 - parameter of fetal well-being vs. distress
- **Variability**
 - physiologic variability is a normal characteristic of FHR
 - effect of vagus nerve on fetal heart
 - normal variability indicates fetal acid-base status is acceptable
 - can only be assessed by electronic fetal monitoring (CTG)
 - variability decreases intermittently even in healthy fetus
- **Periodicity**
 - accelerations: increase of ≥ 15 bpm lasting ≥ 15 seconds, in response to fetal movement or uterine contraction (or ≥ 10 bpm lasting ≥ 10 sec if < 32 wks GA)
 - decelerations: 3 types, described in terms of shape, onset, depth, duration recovery, occurrence, and impact on baseline FHR and variability (see Table 18)

Table 17. Factors Affecting Fetal Heart Rate

	Fetal Tachycardia (FHR > 160)	Fetal Bradycardia (FHR < 110)	Decreased Variability
Maternal Factors	Fever Hyperthyroidism Anemia	Hypothermia Hypotension Hypoglycemia	Infection Dehydration
Fetal Factors	Arrhythmia Anemia	Rapid descent Dysrhythmia Heart block	CNS anomalies Dysrhythmia Inactivity/sleep cycle, preterm fetus
Drugs	Sympathomimetics	β -blockers Anesthetics	Narcotics, sedatives Magnesium sulphate, β -blockers
Uteroplacental	Early hypoxia (abruption, HTN) Chorioamnionitis	Late hypoxia (abruption, HTN) Acute cord prolapse Hypercontractility	Hypoxia

Fetal Scalp Blood Sampling

- indicated when non-reassuring fetal heart rate (NRFHR) is suggested by clinical parameters including heavy meconium or moderately to severely abnormal FHR patterns, including unexplained low variability, repetitive late decelerations, complex variable decelerations, fetal cardiac arrhythmias
 - pH ≥ 7.25 : normal, repeat if abnormal FHR persists
 - pH 7.21-7.24: repeat assessment in 30 minutes or consider delivery if rapid fall since last sample
 - pH ≤ 7.20 : indicates fetal acidosis, delivery is indicated
- contraindications
 - known or suspected fetal blood dyscrasia (hemophilia, von Willebrand disease)
 - active maternal infection (HIV, genital herpes)



Continuous Cardiotocography (CTG) as a Form of Electronic Fetal Monitoring (EFM) for Fetal Assessment during Labour

Cochrane Database of Systematic Reviews 2006, Issue 3

Purpose: To examine the effectiveness of continuous fetal heart monitoring (cardiotocography) during labour on improving health outcomes.

Methods: Systematic review comparing continuous fetal monitoring with no monitoring, intermittent auscultation, and intermittent monitoring.

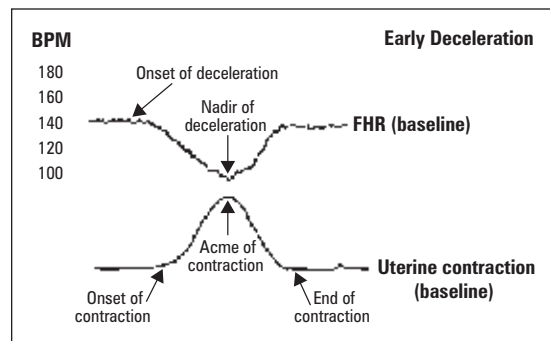
Results: 12 trials (37 000 women) meeting search criteria were identified, of which 2 trials were high quality. Continuous electronic fetal heart monitoring did not have an effect on overall perinatal death rate compared to intermittent auscultation, with a relative risk (RR) of 0.85, 95% CI 0.59-1.23. Continuous monitoring also led to increased incidence of C-section (RR 1.66, 95% CI 1.30 to 2.13, $n = 18,761$, 10 trials) and instrument assisted vaginal delivery (RR 1.16, 95% CI 1.01 to 1.32, $n = 18,151$, nine trials). These results appeared consistent regardless if pregnancy was high risk, low risk, or pre-term.

Summary: Continuous fetal cardiotocography does not significantly improve infant mortality or other standards of infant well-being. It increases the incidence of C-section and instrument assisted vaginal delivery.

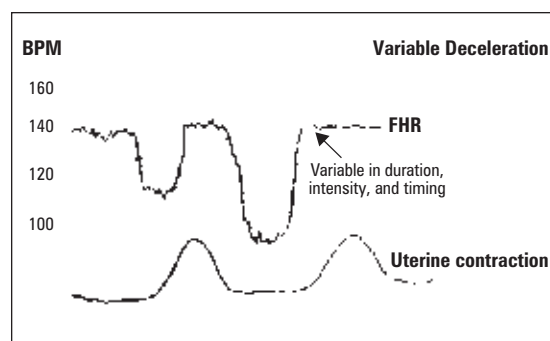
Table 18. Comparison of Decelerations

Early Decelerations

- Uniform shape with onset early in contraction; returns to baseline by end of contraction, mirrors contraction
- Gradual deceleration
- Often repetitive; no effect on baseline FHR or variability
- Benign, due to vagal response to head compression

**Variable Decelerations**

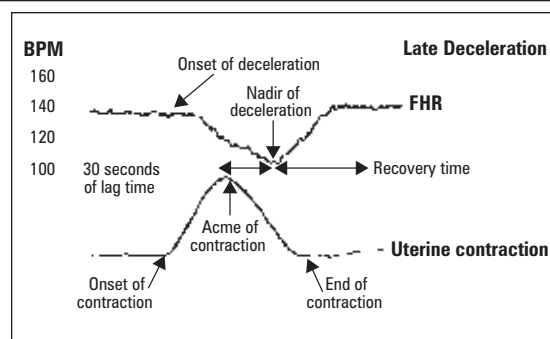
- Variable in shape, onset, and duration
- Most common type of periodicity seen during labour
- Often with abrupt drop in FHR; usually no effect on baseline FHR or variability
- Due to cord compression or, in second stage, forceful pushing with contractions

**Complicated Variable Decelerations**

- To <70 bpm for >60 sec
- Loss of variability or decrease in baseline after deceleration
- Biphasic deceleration
- Slow return to baseline
- Baseline tachycardia or bradycardia

Late Decelerations

- Uniform shape with onset late in contraction, nadir after peak of contraction, and slow return to baseline
- May cause decreased variability and change in baseline FHR
- Due to fetal hypoxia and acidemia, maternal hypotension or uterine hypertonus
- Usually a sign of uteroplacental insufficiency (an ominous sign)

**Rule of 60's Suggesting Severe****Variable Decelerations:**

Deceleration to <60 bpm
>60 bpm below baseline
>60 sec in duration with slow return to baseline

**Approach to the Management of Abnormal FHR**

Ensure fetal tracing
Call for help
Change position to LLDP
100% O₂ by mask
Stop oxytocin
Correct maternal hypotension
Fetal scalp pH/fetal scalp electrode
Vaginal exam to rule out cord prolapse
Rule out fever, dehydration, drug effects, prematurity
Amnioinfusion or tocolytics in selected cases
C/S when necessary

Table 19. Classification of Intrapartum EFM Tracings

	Normal Tracing (Category 1)	Atypical Tracing* (Category 2)	Abnormal Tracing* (Category 3)
Baseline	110-160 bpm	Bradycardia 100-100 bpm Tachycardia >160 for 30-80 min Rising baseline	Bradycardia <100 bpm Tachycardia >160 bpm for >80 min Erratic baseline
Variability	6-25 bpm ≤5 bpm for <40 min	≤5 bpm for 40-80 min	<5 bpm for >80 min ≥25 bpm for >10 min
Decelerations	None Early decelerations Occasional uncomplicated variable decelerations	Repetitive (≥3) uncomplicated variable decelerations Occasional late decelerations Any prolonged deceleration 2-3 min	Repetitive (≥3) complicated variable decelerations Repetitive late decelerations Any prolonged deceleration >3 min
Accelerations	Accelerations spontaneous or during scalp stimulation	Absent with scalp stimulation	Nearly absent
Action	EFM may be interrupted for ≤30 min if mother/fetus stable	Further assessment required	Action required: review clinical situation, obtain scalp pH, prepare for possible delivery

Adapted from SOGC guidelines, September 2008

*Previous classification was "reassuring" vs. "non-reassuring", but distinction is now made between tracings that have some concerning changes but do not require immediate action (atypical) versus those with major concerns requiring immediate intervention (abnormal).

Fetal Oxygenation

- uterine contractions during labour decrease uteroplacental blood flow, which results in reduced oxygen delivery to the fetus
- most fetuses tolerate this reduction in flow and have no adverse effects
- distribution of oxygen to the fetus depends on maternal, uteroplacental and fetal factors
- maternal factors**
 - decreased maternal oxygen carrying capacity
 - significant anemia (iron deficiency, hemoglobinopathies)
 - carboxyhemoglobin (smokers)
 - decreased uterine blood flow
 - hypotension (blood loss, sepsis)
 - regional anesthesia
 - maternal positioning
 - chronic maternal conditions
 - vasculopathies (lupus, Type 1 DM, chronic HTN)
 - antiphospholipid syndrome
 - cyanotic heart disease
 - COPD
- uteroplacental factors**
 - uterine hypertonus
 - hyperstimulation secondary to oxytocin, prostaglandins or normal labour
 - placental abruption
 - uteroplacental dysfunction
 - placental abruption
 - placental infarction (dysfunction marked by IUGR, oligohydramnios, abnormal Doppler studies)
 - chorioamnionitis
 - placental edema (diabetes, hydrops)
 - placental senescence (post dates)
- fetal factors**
 - cord compression
 - oligohydramnios
 - cord prolapse or entanglement
 - decreased fetal oxygen carrying capability
 - significant anemia (isoimmunization, feto-maternal bleed)
 - carboxyhemoglobin (exposure to smokers)
- fetal response to hypoxia/asphyxia**
 - decreased movement, tone, and breathing activities
 - redistribution of fetal blood flow
 - increased flow to brain, heart, and adrenals
 - decreased flow to kidneys, lungs, gut, liver and peripheral tissues
 - increase in blood pressure
 - transient fetal bradycardia followed by fetal tachycardia
 - anaerobic metabolism (decreased pH)

Induction of Labour

Definition

- artificial initiation of labour before its spontaneous onset for the purpose of delivery of the fetus and placenta

Prerequisites for Labour Induction

- capability for C/S if necessary
- maternal
 - short, thin, soft, anterior cervix with open os (“inducible” or “ripe”)
 - if cervix is not ripe, use prostaglandin vaginal insert (Cervidil®), prostaglandin gel (Prepidil®), or Foley catheter
- fetal
 - reassuring fetal heart tracing
 - cephalic presentation
 - adequate fetal monitoring available
- likelihood of success determined by Bishop score (see Table 20)
 - cervix considered unfavourable if <6
 - cervix favourable if ≥6
 - score of 9-13 associated with high likelihood of vaginal delivery



Induction vs. Augmentation

Induction is the artificial initiation of labour.

Augmentation promotes contractions when spontaneous contractions are inadequate.



Induction is indicated when the risk of continuing pregnancy exceeds the risks associated with induced labour and delivery.

Table 20. Bishop Score

Cervical characteristic	0	1	2	3
Position	Posterior	Mid	Anterior	–
Consistency	Firm	Medium	Soft	–
Effacement (%)	0-30	40-50	60-70	≥80
Dilatation (cm)	0	1-2	3-4	≥5
Station of fetal head	-3	-2	-1, 0	+1, +2



Consider the Following before Induction

- Indication for induction
- Contraindications
- GA
- Cervical favourability
- Fetal presentation
- Potential for CPD
- Fetal well-being/FHR
- Membrane status

Indications

- post-date pregnancy (generally >41 weeks)
- maternal factors
 - significant antepartum hemorrhage
 - gestational HTN
 - other maternal medical problems, e.g. diabetes, renal or lung disease
- maternal-fetal factors
 - isoimmunization, PROM, chorioamnionitis, post-term pregnancy
- fetal factors
 - suspected fetal jeopardy as evidenced by biochemical or biophysical indications
 - fetal demise, severe IUGR

Risks

- failure to achieve labour and/or vaginal birth
- uterine hyperstimulation and fetal compromise
- uterine rupture
- uterine atony and PPH
- maternal side effects to medications

Contraindications

- maternal
 - prior classical or inverted-T incision or uterine surgery (e.g. myomectomy)
 - unstable maternal condition
 - gross CPD (although diagnosis cannot be made until active labour)
 - active maternal genital herpes
 - invasive cervical carcinoma
 - pelvic structure deformities
- maternal-fetal
 - placenta previa or vasa previa
 - cord presentation
- fetal
 - fetal distress, malpresentation, preterm fetus without lung maturity



Evidence for Cervical Ripening Methods (SOGC Guidelines)

- Meta-analysis of five trials has concluded that the use of oxytocin to ripen the cervix is not effective.
- Since the best dose and route of misoprostol for labour induction with a live fetus are not known and there are concerns regarding hyperstimulation, the use of misoprostol for induction of labour should be within clinical trials only (Level Ib evidence) or in cases of intrauterine fetal death to initiate labour.

Use of Prostaglandins in Cervical Ripening and Induction Intravenous Prostaglandin for Induction of Labour

- Prostaglandin E2 and F2 alpha can be used for cervical ripening and induction of labour. A meta-analysis comparing intravenous prostaglandin with oxytocin concluded that intravenous prostaglandin was no more likely to result in vaginal delivery (RR 0.85). Prostaglandins were associated with significantly more maternal side effects including gastrointestinal problems, thrombophlebitis and pyrexia. Currently, there is not enough evidence to draw any conclusions about the relative effects of prostaglandins vs. oxytocin and the choice is between the patient and the physician.
- Intravaginal prostaglandins are associated with higher rate of uterine hypertonus, uterine hyperstimulation, and fetal heart rate abnormalities.
- Prostaglandins are associated with reduced rate of C/S, instrumental vaginal delivery, and failed induction.

Cochrane Review. The Cochrane Library, 2000. Issue 2

Induction Methods

CERVICAL RIPENING

Definition

- use of medications or other means to soften, efface and dilate cervix to increase likelihood of induction success
- ripening of an unfavourable cervix (Bishop score <6) is warranted prior to induction of labour

Methods

- intravaginal prostaglandin PGE2 gel (Prostin® gel): long and closed cervix with no ROM
 - recommended dosing interval of prostaglandin gel is every 6 to 12 hours up to 3 doses
- intravaginal PGE2 (Cervidil®): long and closed cervix, may use if ROM
 - continuous release, can be removed if needed
 - controlled release PGE2
- Foley catheter placement to mechanically dilate the cervix
- hydroscopic dilators, osmotic dilators (laminaria)
- misoprostol: synthetic methylated PGE1 (not commonly used)

INDUCTION OF LABOUR

Amniotomy

- artificial rupture of membranes (amniotomy) to stimulate PG synthesis and secretion; may try this as initial measure if cervix is dilated
- few studies address the value of amniotomy alone for induction of labour
- amniotomy plus intravenous oxytocin: more women delivered vaginally at 24 hours than amniotomy alone (relative risk = 0.03) and had fewer instrumental vaginal deliveries (relative risk = 5.5)

Oxytocin

- oxytocin (Pitocin®): 10 U in 1L NS, run at 0.5-2 mU/min IV increasing by 1-2 mU/min q20-60 min to a max of 36-48 mU/min
 - reduces rate of unsuccessful vaginal deliveries within 24 hours when used alone (8.3% vs. 54%, RR 0.16)
 - ideal dosing regime of oxytocin is not known
 - current recommendations: use the minimum dose to achieve active labour and increase every 30 minutes as needed
 - reassessment should occur once a dose of 20 mU/min is reached
- potential complications
 - hyperstimulation/tetanic contraction (may cause fetal distress or rupture of uterus)
 - uterine muscle fatigue, uterine atony (may result in PPH)
 - vasopressin-like action causing anti-diuresis



Intravaginal PGE2 (Cervidil™) Compared to Intravaginal Prostaglandin Gel

4 RCTs have compared the two with varying results, depending on the dosing regime of gel used.

Theoretical advantages of Cervidil®:

- Insertion without a speculum
- Slow, continuous release
- Only one dose required
- Ability to use oxytocin 30 min. after removal
- Ability to remove insert if required (i.e. excessive uterine activity)



Oxytocin $t_{1/2}$ = 3-5 minutes.

Augmentation of Labour

- augmentation of labour is used to promote adequate contractions when spontaneous contractions are inadequate and cervical dilatation or descent of fetus fails to occur
- oxytocin (0.5-2 mU/min IV increasing by 1-2 mU/min q20-60 min to a max of 36-48 mU/min)

High Risk Labour and Delivery



Preterm Labour (PTL)

Definition

- labour occurring between 20 and 37 weeks gestation

Etiology

- idiopathic (most common)
- maternal:** infection (recurrent pyelonephritis, untreated bacteriuria, chorioamnionitis), genital infection (bacterial vaginosis is associated with a twofold increase in relative risk of preterm birth), HTN, DM, chronic illness, mechanical factors, previous obstetric, gynecological and abdominal surgeries, socio-environmental (poor nutrition, smoking, drugs, alcohol, stress)
- maternal-fetal:** PPROM (common), polyhydramnios, placenta previa or abruption, placental insufficiency
- fetal:** multiple gestation, congenital abnormalities of fetus, fetal hydrops
- uterine:** incompetent cervix, excessive enlargement (hydramnios), malformations (leiomyomas, septate uterus)

Epidemiology

- preterm labour complicates about 10% of pregnancies

Risk Factors and Prediction of PTL

- maternal risk scoring using above etiologies fails to identify up to 70% of preterm deliveries and is therefore of limited use
- prior history of spontaneous PTL – most important risk factor
- prior history cervical excisions or mechanical dilatation
- cervical length – measured by TV U/S (cervical length >30 mm has high negative predictive value for PTL before 34 weeks)
- identification of bacterial vaginosis (Rx – metronidazole) and ureaplasma urealyticum (Rx – erythromycin) infections – routine screening not supported by current data but it is reasonable to screen high risk women
- fetal fibronectin – a glycoprotein in amniotic fluid and placental tissue functioning to maintain integrity of chorionic-decidual interface in asymptomatic women
 - positive if >50 ng/mL
 - in symptomatic women (i.e. preterm contractions), fetal fibronectin is most effectively combined with U/S detecting cervical length
 - if cervical length is not short and fetal fibronectin is negative, preterm labour is highly unlikely



PTL Recurrence

Definition: 3 or more consecutive lost pregnancies prior to 20th week of gestation

- 15% sporadic loss of 1 pregnancy
- 2% experience 2 consecutive pregnancy losses
- 0.4-1% experience 3 consecutive pregnancy losses



Positive fetal fibronectin in cervicovaginal fluid (>50 ng/mL) at 24 weeks gestation predicted spontaneous PTL at <34 weeks with sensitivity of 23%, specificity of 97%, PPV of 25%, NPV of 96%

Clinical Features

- regular contractions (2 in 10 minutes)
- cervix >2 cm dilated or 80% effaced or documented change in cervix

Management**A. Initial**

- transfer to appropriate facility if stable
- hydration (NS at 150 mL/hour)
- bed rest in LLD
- sedation (morphine)
- avoid repeated pelvic exams (increased infection risk)
- U/S examination of fetus (GA, BPP, position, placenta location, estimated fetal weight)
- prophylactic antibiotics; controversial but may help delay delivery, important to consider if PPRM

B. Suppression of Labour – Tocolysis

- does not inhibit preterm labour completely, but may buy time to allow for betamethasone valerate (Celestone®) and/or transfer to appropriate centre
- requirements (all must be satisfied)
 - preterm labour
 - live, immature fetus, intact membranes, cervical dilatation of <4 cm
 - absence of maternal or fetal contraindications
- contraindications
 - maternal: bleeding (placenta previa or abruption), maternal disease (hypertension, diabetes, heart disease), preeclampsia or eclampsia, chorioamnionitis
 - fetal: erythroblastosis fetalis, severe congenital anomalies, fetal distress/demise, IUGR, multiple gestation (relative)
- tocolytic procedure
 - ensure availability of necessary personnel and equipment to assess mother and fetus during labour and care for baby of the predicted GA if therapy fails
 - if no contraindications present, agent used depends on clinical situation
 - should be used only for <48 hr and/or until transfer to an appropriate facility for care of the premature infant
 - proven efficacy
 - ♦ first line: calcium channel blockers: nifedipine
 - ♦ second line: prostaglandin (PG) synthesis inhibitors: indomethacin
 - ♦ some emerging evidence for use of progesterone
 - no proven efficacy
 - ♦ nitroglycerin patch: vasodilator and smooth muscle relaxant
 - ♦ magnesium sulfate (if diabetes or cardiovascular disease present)

C. Enhancement of Fetal Pulmonary Maturity

- betamethasone valerate (Celestone®) 12 mg IM q24h x 2 or dexamethasone 6 mg IM q12h x 4
 - 28-34 weeks GA: reduces incidence of respiratory distress syndrome (RDS)
 - 24-28 weeks GA: reduces severity of RDS, overall mortality and rate of intraventricular hemorrhage (IVH)
 - specific maternal contraindications: active TB, viral keratitis, maternal DM

D. Cervical Cerclage

- definition: placement of cervical sutures, wires or synthetic tape at the level of the internal os, usually at the end of the first trimester and removed in the third trimester
- indications: cervical incompetence (i.e. cervical dilation and effacement in the absence of increased uterine contractility)
 - emerging evidence indicates that progesterone suppositories are superior to cerclage in preventing preterm labor late in pregnancy
- diagnosis of cervical incompetence
 - obstetrical Hx: silent cervical dilation
 - ability of cervix to hold an inflated Foley catheter during a hysterosonogram
- proven benefit in the prevention of PTL in women with primary structural abnormality of the cervix (e.g. conization of the cervix, connective tissue disorders)
- benefit is variable in those with secondary cervical incompetence causing premature ripening of the cervix (e.g. infection, abnormal placentation)

Prognosis

- prematurity is the leading cause of perinatal morbidity and mortality
 - 30 weeks or 1500 g (3.3 lb) = 90% survival
 - 33 weeks or 2000 g (4.4 lb) = 99% survival
- morbidity due to asphyxia, hypoxia, sepsis, respiratory distress syndrome (RDS), intraventricular cerebral hemorrhage, thermal instability, retinopathy of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis

Prevention of Preterm Labour

- currently there are no agents approved by Health Canada to arrest preterm labour
- preventative measures: good prenatal care, identify pregnancies at risk, treat silent vaginal infection or UTI, patient education
- transvaginal ultrasound of cervical length is recommended only for high-risk pregnancies

Premature Rupture of Membranes (PROM)**Definitions**

- premature ROM (PROM or amniorrhexis): rupture of membranes prior to labour at any GA
- prolonged ROM: >24 hours elapsed between rupture of membranes and onset of labour
- preterm ROM: ROM occurring before 37 weeks gestation (associated with PTL)
- preterm premature ROM (PPROM): rupture of membranes before 37 weeks AND prior to onset of labour

Risk Factors

- maternal: multiparity, cervical incompetence, infection (cervicitis, vaginitis, STI, UTI), family history of PROM, low socioeconomic class/poor nutrition
- fetal: congenital anomaly, multiple gestation
- other risk factors associated with PTL

Clinical Features

- history of fluid gush or continued leakage

Investigations

- sterile speculum exam (avoid introduction of infection)
 - pooling of fluid in the posterior fornix
 - may observe fluid leaking out of cervix on cough/Valsalva ("cascade")
- nitrazine (amniotic fluid turns nitrazine paper blue)
 - low specificity as can be positive with blood, urine or semen
- ferning (high salt in amniotic fluid evaporates, looks like ferns under microscope)
- U/S to rule out fetal anomalies, assess GA and BPP

**Membrane Status Determined by**

- Pooling of fluid on speculum exam
- Increase pH of vaginal fluid (nitrazine test)
- Ferning of fluid under light microscopy
- Decreased AFW on U/S

Management

- admit for expectant management and monitor vitals q4h, daily BPP and WBC count
- avoid introducing infection with examinations (do NOT do a bimanual exam)
- cultures (cervix for GC, lower vagina for GBS)
- assess fetal lung maturity by L/S ratio of amniotic fluid
 - consider administration of betamethasone valerate (Celestone®) to accelerate maturity if <32 weeks and no evidence of infection
 - consider tocolysis for 48h to permit administration of steroids if PPROM induces labour
- weigh degree of prematurity vs. risk of amnionitis and sepsis by remaining in utero
 - <24 weeks: consider termination (poor outcome due to pulmonary hypoplasia)
 - 24-25 weeks: individual consideration with counselling of parents re: risks to preterm infants
 - 26-34 weeks: expectant management as prematurity complications are significant
 - 34-36 weeks: "grey zone" where risk of death from RDS and neonatal sepsis is the same
 - ≥37 weeks: induction of labour since the risk of death from sepsis is greater than RDS
- if not in labour or labour not indicated, consider antibiotics (controversial)
 - studies show broad spectrum coverage increases the time to onset of labour from PROM by 5-7 days with no increase in maternal or neonatal morbidity or mortality
- deliver urgently if evidence of fetal distress and/or chorioamnionitis

Prognosis

- varies with gestational age
 - 90% of women with PROM at 28-34 weeks GA go into spontaneous labour within 1 week
 - 50% of women with PROM at <26 weeks GA go into spontaneous labour within 1 week
- complications: cord prolapse, intrauterine infection (chorioamnionitis), premature delivery, limb contracture

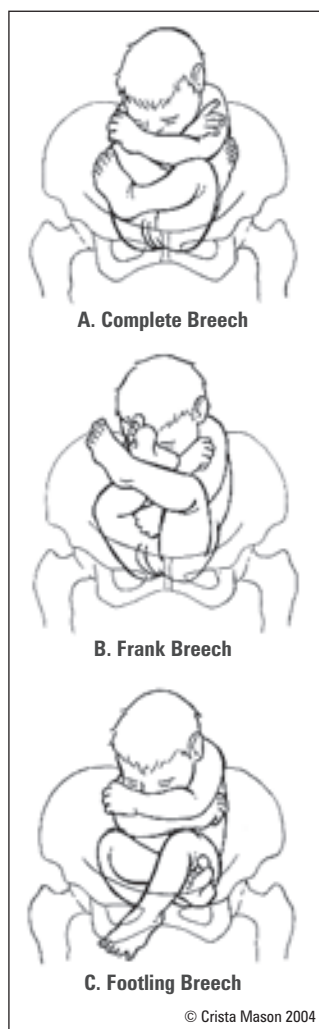


Figure 8. Types of Breech Presentation

Vaginal Delivery of Breech Presentation

SOGG Clinical Practice Guideline, JOGC, June 2009
Objective: To discuss risks and benefits of trial of labour versus planned C-section, with selection criteria, management and delivery techniques for trial of vaginal breech birth.

Evidence: Randomized trials, prospective cohort studies and select cohort studies from Medline search for long-term outcomes and epidemiology of vaginal breech delivery.

Summary: Higher risk of perinatal mortality and short-term neonatal morbidity can be associated with vaginal breech birth as compared to elective C-sections. However, careful case selection (including term singleton breech fetuses and clinically adequate maternal pelvis) and labour management may achieve a similar safety level as elective C-sections (approx. 2 per 1000 births perinatal mortality, approx. 2% short-term neonatal morbidity). Specific protocols for vaginal breech delivery should be followed: continuous fetal heart monitoring, assessment for adequate progress in labour, no induction of labour recommended, emergency C-section available if required and health care providers with requisite skills and experience. Informed consent for the preferred delivery method should be obtained.

Breech Presentation

Definition

- fetal buttocks or lower extremity is the presenting part (see Figure 8)
- complete (10%): flexion at hips and knees
- frank (60%): flexion at hips, extension at knees
 - most common type of breech presentation
 - most common breech presentation to be delivered vaginally
- footling (30%): may be single or double with extension at hip(s) and knee(s) so that foot is the presenting part

Epidemiology

- occurs in 3-4% of pregnancies at term (25% before 28 weeks)

Risk Factors

- maternal risk factors
 - pelvis (contracted)
 - uterus (shape abnormalities, intrauterine tumours, fibroids)
 - extrauterine tumours causing compression
 - grand multiparity
- maternal-fetal
 - placenta (previa)
 - amniotic fluid (poly/oligohydramnios)
- fetal
 - prematurity
 - multiple gestation
 - congenital malformations (found in 6% of breeches; 2-3% if in vertex presentations)
 - abnormalities in fetal tone and movement
 - aneuploidy

Clinical Features

- noted by Leopold's maneuvers (see Figure 2) and U/S
 - PPV of Leopold's maneuvers is only 30%

Management

- external cephalic version (ECV): repositioning of fetus within uterus under U/S guidance
 - overall success rate of 65%
 - criteria: >37 weeks, singleton, unengaged presenting part, reactive NST
 - contraindications: previous T3 bleed, prior classical C/S, previous myomectomy, oligohydramnios, PROM, placenta previa, abnormal U/S, suspected IUGR, hypertension, uteroplacental insufficiency, nuchal cord
 - risks: abruption, cord compression
 - method: tocometry, followed by ultrasound guided transabdominal manipulation of fetus with consistent fetal heart monitoring
 - if patient Rh negative, give Rhogam® prior to procedure
 - good prognostic factors (for a successful version)
 - ♦ multiparous, good fluid volume, small baby, skilled obstetrician
- pre- or early labour ultrasound to assess type of breech presentation, fetal growth, estimated weight, altitude of fetal head; if ultrasound unavailable, recommend C-section
- trial of labour and elective C-section should be presented as options with the risks and benefits outlined; obtain informed consent
- contraindications to vaginal breech delivery:
 - cord presentation
 - clinically inadequate maternal pelvis
 - fetal anomaly incompatible with vaginal delivery
- criteria for vaginal breech delivery:
 - frank or complete breech, GA >36 weeks
 - EFW 2500-3800 g based on clinical and U/S assessment (5.5-8.5 lb)
 - fetal head flexed
 - continuous fetal monitoring
 - 2 experienced obstetricians, assistant, and anesthetist present
 - ability to perform emergency C-section within 30 minutes if required
- method for vaginal breech delivery:
 - encourage effective maternal pushing efforts
 - at delivery of after-coming head, assistant must apply suprapubic pressure to flex and engage fetal head
 - delivery can be spontaneous or assisted; avoid fetal traction
 - apply fetal manipulation only after spontaneous delivery to level of umbilicus
- C/S recommended if: the breech has not descended to the perineum in the second stage of labour after 2 hours, in the absence of active pushing, or if vaginal delivery is not imminent after 1 hour of active pushing

Prognosis

- regardless of route of delivery, breech infants have lower birth weights and higher rates of perinatal mortality, congenital anomalies, abruption and cord prolapse

Vaginal Birth After Caesarean (VBAC)

- recommended after previous low transverse incision
- success rate varies with indication for previous C/S (generally 60-80%)
- risk of uterine rupture (<1% with low transverse incision)

Contraindications

- previous classical, inverted-T, or unknown uterine incision, or complete transection of uterus (6% risk of rupture)
- history of hysterotomy or previous uterine rupture
- multiple gestation
- estimated fetal weight >4000 g (9 lb)
- non-vertex presentation or placenta previa
- inadequate facilities or personnel for emergency C/S

**Vaginal Delivery After C-Section (VBAC)**

- Rate of VBAC ranges from 60-82%
- No significant difference in maternal deaths or hysterectomies between VBAC or C-section
- Uterine rupture more common in VBAC group
- Evidence regarding fetal outcome is lacking

Safety of vaginal birth after caesarean section: a systematic review. *Obstet Gynecol* 2004; 103(3):420-9

Prolonged Pregnancy**Definition**

- pregnancy beyond 42 weeks GA

Epidemiology

- 41 weeks GA: up to 27%
- 42 weeks GA: 4-14%

Etiology

- most cases idiopathic
- anencephalic fetus with no pituitary gland
- placental sulfatase deficiency (X-linked recessive condition in 1/2000-1/6000 infants)

Clinical Features

- postmaturity syndrome: 10-20% of post-term pregnancies (fetal weight loss, reduction in subcutaneous fat, scaling, dry skin from placental insufficiency, long thin body, open-eyed, alert and worried look, long nails, palms and soles wrinkled)
- with increasing GA, higher rates of: intrauterine infection, asphyxia, meconium aspiration syndrome, placental insufficiency, placental aging and infarction, macrosomia, dystocia, fetal distress, operative deliveries

Management

- GA 40-41 weeks – expectant management
 - no evidence to support induction of labour (IOL) or C/S unless other risk factors for morbidity are present (see prognosis)
- GA >41 weeks – offer induction of labour (IOL) if vaginal delivery is not contraindicated
 - IOL shown to decrease C/S, fetal heart rate changes, meconium staining, macrosomia and death when compared with expectant management
- GA >41 weeks and expectant management elected – serial fetal surveillance:
 - fetal movement count by the mother
 - AFV ± NST (modified BPP)

Prognosis

- if >41 weeks, perinatal mortality 2-3x higher (due to progressive uteroplacental insufficiency)
- morbidity increased with hypertension in pregnancy, DM, abruption, IUGR and multiple gestation

Intrauterine Fetal Death**Definition**

- fetal death in utero after 20 weeks GA

Epidemiology

- 1% of pregnancies



DIC: Generalized coagulation and fibrinolysis leading to depletion of coagulation factors

Obstetrical Causes

- Abruptio
- PIH
- Fetal demise
- PPH

DIC-specific Bloodwork

- Platelets
- aPTT and PT
- FDP (fibrin degradation products)
- Fibrinogen

Treatment

- Treat underlying cause
- Supportive
 - Fluids
 - Blood products
 - FFP, platelets, cryoprecipitate
- Consider anti-coagulation as VTE prophylaxis

Etiology

- 50% idiopathic
- 50% secondary to HTN, DM, erythroblastosis fetalis, congenital anomalies, umbilical cord or placental complications, intrauterine infection, APLA syndrome

Clinical Features

- decreased perception of fetal movement by mother
- SFH and maternal weight not increasing
- absent fetal heart tones (not diagnostic)
- high maternal serum alpha-fetoprotein (MSAFP)

Management

- diagnosis: absent cardiac activity and fetal movement on U/S required for diagnosis
- determine secondary cause
 - maternal: HbA_{1c}, Kleihauer-Betke, VDRL, ANA, antibody screens, INR/PTT, serum/urine toxicology screens, cervical and vaginal cultures, TORCH screen
 - fetal: chromosomes, cord blood, skin biopsy, genetics evaluation, autopsy
 - placenta: pathology, bacterial cultures

Treatment

- induction of labour
- monitor for maternal coagulopathy [10% risk of disseminated intravascular coagulation (DIC)]
- parental psychological care:
 - referral to grieving support programs
 - encourage partner to stay for support, ask couple to hold the newborn (inform that bruising, facial marks may be present)
 - make neonatal footprint, take a photo of the newborn, encourage to name the child
 - early follow-up within 2 weeks to assess mental well-being (depression, anxiety)
 - comprehensive discussion within 3 months about final investigation and post-mortem results, help make plans for future pregnancies



Complications of Labour and Delivery

Meconium in Amniotic Fluid

Epidemiology

- usually not present early in labour
- in general, meconium may be present in up to 25% of all labours; usually NOT associated with poor outcome, but extra care is required at time of delivery to avoid aspiration

Etiology

- likely cord compression ± uterine hypertonus
- may indicate undiagnosed breech
- increasing meconium during labour may be a sign of fetal distress

Clinical Features

- timing: early (prior to ROM) or late (after ROM with clear fluid)
- consistency
 - thin meconium: light green or yellow, not usually associated with poor outcome
 - thick meconium: dark green or black, pea-soup consistency, associated with lower APGARs and increased risk of meconium aspiration

Treatment

- call respiratory therapy, neonatology or pediatrics to delivery room
- oropharynx suctioning upon head expulsion or immediately after delivery if baby not breathing spontaneously (do NOT stimulate infant before)
- consider amnioinfusion of ~800 mL of IV NS over 50-80 min during active stage of labour and a maintenance dose of ~3 mL/min until delivery
- closely monitor FHR for signs of fetal distress

Abnormal Progression of Labour (Dystocia)

Definition

- expected patterns of descent of the presenting part and cervical dilatation fail to occur in the appropriate time frame; can occur in all stages of labour (see Figure 9)
- during active phase: >4 hrs of <0.5 cm/hr
- during 2nd phase: >1 hr with no descent during active pushing



Maternal Mortality Causes

- Thrombo-embolism
- Cardiac event
- Suicide
- Sepsis
- Ectopic pregnancy
- Hypertension
- Amniotic-fluid embolism
- Hemorrhage

* In Canada (2005), lifetime risk of maternal death is 1 in 11,000



Dark green or black meconium is associated with lower APGARs and increased risk of meconium aspiration.

Etiology

- **Power** (leading cause): contractions (hypotonic, incoordinate), inadequate maternal expulsive efforts
- **Passenger**: fetal position, attitude, size, anomalies (hydrocephalus)
- **Passage**: pelvic structure (cephalopelvic disproportion), maternal soft tissue factors (tumours, full bladder or rectum, vaginal septum)
- **Psyche**: hormones released in response to stress can bring about dystocia
 - psychological and physiological stress should be evaluated as part of the management once dystocia has been diagnosed

**The 4 Ps of Dystocia**

Power
Passenger
Passage
Psyche

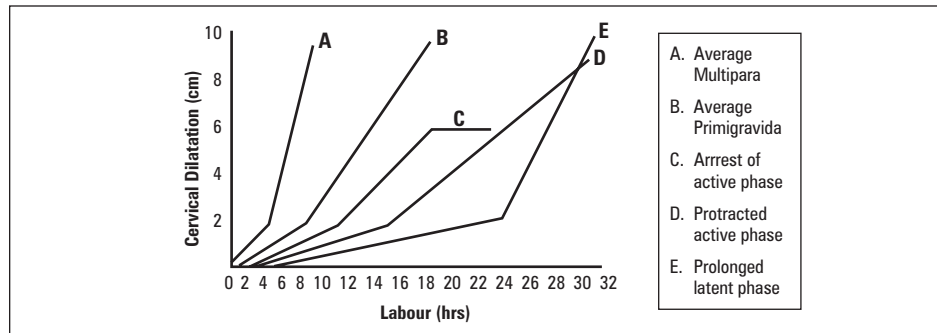


Figure 9. Normal and Abnormal Courses of the First Stage of Labour

Arrest Disorder (Curve C)

- arrest of dilatation
 - dilatation progress does not occur for ≥ 2 hrs in a patient who has entered the active phase
 - arrest usually occurs at a cervical dilatation of 5-8 cm
- arrest of descent
 - no progress in station for >1 hr during second stage
 - should search for factors causing CPD (nearly 50% require C/S)
 - CPD diagnosed if adequate contractions measured by intrauterine pressure catheter (IUPC) with no descent/dilatation for >2 hours
 - if CPD ruled out, IV oxytocin and amniotomy can be attempted

Protraction Disorders (Curve D)

- protraction of dilatation: slope of cervical dilatation <1.2 cm/hr in primigravidas or <1.5 cm/hr in multigravidas
- protraction of descent: a rate of descent of <1.0 cm/hr in primigravidas or 2.0 cm/hr in multigravidas
- treatment: oxytocin augmentation if contractions are inadequate \pm amniotomy

Prolonged Latent Phase (Curve E)

- ≥ 20 hrs in primigravidas or ≥ 14 hrs in multigravidas during which labour has not progressed to the active phase
- most often due to false labour (avoid amniotomy for fear of false labour and increased risk of intrauterine infection)
- premature or excessive use of sedation or analgesia may play a role
- careful search for factors of CPD should be made
- management: oxytocin augmentation if diagnosis of labour is certain, otherwise rest \pm sedation

Risks of Dystocia

- inadequate progression of labour is associated with an increased incidence of:
 - maternal stress
 - maternal infection
 - postpartum hemorrhage
 - need for neonatal resuscitation

**The 4 Types of Pelvis****GAAP**

Gynecoid (50%) – commonest, obstetrically ideal
 Anthropoid (25%)
 Android (20%)
 Platypelloid (5%)



- 1/3 of protraction disorders develop into 2^o arrest of dilatation due to CPD
- 2/3 of protraction disorders progress through labour to vaginal delivery

Umbilical Cord Prolapse

Definition

- descent of the cord to a level adjacent to or below the presenting part, causing cord compression between presenting part and pelvis

Etiology/Epidemiology

- increased incidence with prematurity/PROM, fetal malpresentation (~50% of cases), low-lying placenta, polyhydramnios, multiple gestation, CPD
- incidence: 0.17-0.63%

**Umbilical Cord Accident Causes**

Nuchal cord
 Type A (looped)
 Type B (hitched)
 Body loop
 Single artery
 True knot
 Torsion
 Velamentous
 Short cord <35 cm
 Long cord >80 cm

Clinical Features

- visible or palpable cord
- FHR changes (variable decelerations, bradycardia or both)

Treatment

- emergency C/S
- O₂ to mother, monitor fetal heart
- alleviate pressure of the presenting part on the cord by placing digit in vagina (maintain this position until C/S)
- keep cord warm and moist by replacing it into the vagina ± applying warm saline soaks
- position mother in Trendelenburg or knee-to-chest position
- if fetal demise or too premature (<22 weeks), allow labour and delivery

Shoulder Dystocia

Definition

- impaction of anterior shoulder of fetus against symphysis pubis after fetal head has been delivered
- life threatening emergency

Etiology/Epidemiology

- incidence 0.15-1.4% of deliveries
- occurs when breadth of shoulders is greater than biparietal diameter of the head

Risk Factors

- maternal: obesity, diabetes, multiparity
- fetal: prolonged gestation, macrosomia
- labour
 - prolonged 2nd stage
 - prolonged deceleration phase (8-10 cm)
 - instrumental midpelvic delivery

Clinical Features

- “turtle sign”: head delivered but retracts against inferior portion of pubic symphysis
- complications
 - chest compression by vagina or cord compression by pelvis can lead to hypoxia
 - brachial plexus injury (Erb palsy: C5-C7; Klumpke’s palsy: C8-T1)
 - ♦ 90% resolve within 6 months
 - fetal fracture (clavicle, humerus, cervical spine)
 - maternal perineal injury, may result in PPH

Treatment

- goal: to displace anterior shoulder from behind symphysis pubis; follow a stepwise approach of maneuvers until goal achieved (see sidebar)
- other options
 - cleidotomy (deliberate fracture of neonatal clavicle)
 - Zavanelli maneuver: replacement of fetus into uterine cavity and emergent C/S
 - symphysiotomy
 - abdominal incision and shoulder disimpaction via hysterotomy – subsequent vaginal delivery

Prognosis

- 1% risk of long term disability for infant

Uterine Rupture

Etiology/Epidemiology

- associated with previous uterine scar (in 40% of cases), hyperstimulation with oxytocin, grand multiparity and previous intrauterine manipulation
- generally occurs during labour, but can occur earlier with a classical incision
- 0.5-0.8% incidence, up to 12% with classical incision

Clinical Features

- prolonged fetal bradycardia – most common presentation
- acute onset abdominal pain
- hyper or hypotonic uterine contractions
- vaginal bleed

**Approach to the Management of Shoulder Dystocia****ALARMER**

Apply suprapubic pressure and ask for help

Legs in full flexion (McRobert’s maneuver)

Anterior shoulder disimpaction (suprapubic pressure)

Release posterior shoulder by rotating it anteriorly with hand in the vagina under adequate anesthesia

Manual corkscrew i.e. rotate the fetus by the posterior shoulder until the anterior shoulder emerges from behind the maternal symphysis

Episiotomy

Rollover (on hands and knees)

*Note that suprapubic pressure and McRobert’s maneuver together will resolve 90% of cases

Treatment

- rule out placental abruption
- immediate delivery for fetal survival
- maternal stabilization (may require hysterectomy)

Complications

- maternal mortality 1-10%
- maternal hemorrhage, shock, DIC
- amniotic fluid embolus
- hysterectomy if uncontrollable hemorrhage
- fetal distress, 50% mortality

Amniotic Fluid Embolus

Definition

- amniotic fluid debris in maternal circulation triggering an anaphylactoid immunologic response

Etiology/Epidemiology

- rare intrapartum or immediate postpartum complication
- 60-80% maternal mortality rate, accounts for 10% of all maternal deaths
- leading cause of maternal death in induced abortions and miscarriages
- 1/8000-1/80,000 births

Risk Factors

- placental abruption
- rapid labour
- multiparity
- uterine rupture
- amniocentesis or uterine manipulation

Differential Diagnosis

- pulmonary embolus, drug-induced anaphylaxis, septic shock, eclampsia, HELLP syndrome, abruption, chronic coagulopathy

Clinical Features

- sudden onset of respiratory distress, cardiovascular collapse (hypotension, hypoxia) and coagulopathy
- seizure in 10%
- ARDS and left ventricular dysfunction seen in survivors

Management

- supportive measures (high flow O₂, ventilation support, fluid resuscitation, inotropic support, ± intubation), coagulopathy correction
- ICU admission

Chorioamnionitis

Definition

- infection of the chorion, amnion and amniotic fluid typically due to ascending infection by organisms of normal vaginal flora

Etiology/Epidemiology

- incidence 1-5% of term pregnancies and up to 25% in preterm deliveries
- may result from hematogenous spread or more commonly, ascending from vagina
- predominant microorganisms include GBS, *Bacteroides* and *Prevotella* species, *E. coli* and anaerobic *Streptococcus*

Risk Factors

- prolonged ROM, long labour, multiple vaginal exams during labour, internal monitoring
- bacterial vaginosis and other vaginal infections

Clinical Features

- maternal fever, maternal or fetal tachycardia, uterine tenderness, foul and purulent cervical discharge

Investigations

- CBC: leukocytosis
- amniotic fluid: leukocytes or bacteria

**Clinical Features of Chorioamnionitis**

Temperature
Tachycardia (maternal or fetal)
Tenderness (uterine)
Foul discharge

Risk Factors for Primary and Subsequent Anal Sphincter Lacerations

Am J Obstet Gynecol 2007; 196(4):344.

Objective: Assess effects of pregnancy, delivery method and parity on risk of primary and secondary anal sphincter laceration in women with 1st vaginal delivery (VD), VBAC or 2nd VD.

Methods: Retrospective cohort study of all deliveries at one hospital from 1995-2002.

Summary: 20,674 live singleton deliveries were included. Women with first VD and VBAC both had OR 5.1 for laceration compared to 2nd VD. Factors that significantly increased risk of laceration for all 3 groups were: forceps and midline episiotomy. 2nd stage of labor >2 h only increased risk for 1st VD. Factors that had no significant increase in risk: infant birth weight >3500g, vacuum delivery. Women with prior anal sphincter laceration are at 3 times increased risk for subsequent sphincter laceration, compared with women with prior vaginal delivery without sphincter laceration.

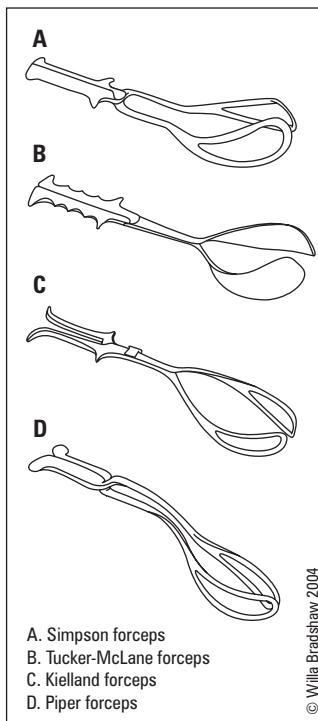


Figure 10. Types of Forceps



Prerequisites for Operative Vaginal Delivery

ABCDEFGHIJK

Anesthesia (adequate)

Bladder empty

Cervix fully dilated and effaced with ROM

Determine position of fetal head

Equipment ready (including facilities for emergent C/S)

Fontanelle (posterior fontanelle midway between thighs)

Gentle traction

Handle elevated

Incision (episiotomy)

once Jaw visible remove forceps

Knowledgeable operator

Treatment

- IV antibiotics (ampicillin and gentamicin and anaerobic coverage if C/S)
- expedient delivery regardless of gestational age

Complications

- bacteremia of mother or fetus, wound infection if C/S, pelvic abscess, infant meningitis

Operative Obstetrics

Operative Vaginal Delivery

Definition

- forceps or vacuum extraction

Indications

- fetal
 - non-reassuring fetal status
 - consider if second stage is prolonged as this may be due to poor contractions or failure of fetal head to rotate
- maternal
 - need to avoid voluntary expulsive effort (e.g. cardiac/cerebrovascular disease)
 - exhaustion, lack of cooperation and excessive analgesia may impair pushing effort

Forceps

Outlet Forceps Position

- head visible between labia in between contractions
- sagittal suture in or close to AP diameter
- rotation cannot exceed 45 degrees

Low Forceps Position

- presenting part at station +2 or greater
- subdivided based on whether rotation less than or greater than 45 degrees

Mid Forceps Position

- presenting part below spines but above station +2
- rarely done

Types of Forceps (see Figure 10)

- Simpson forceps for OA presentations
- Kielland (rotational) forceps when rotation of head to OA is recessing
- Piper forceps for breech

Complications

- maternal: anesthesia risk, lacerations, injury to bladder, uterus or bone, pelvic nerve damage, PPH, infections
- fetal: fractures, facial nerve palsy, trauma to face/scalp, intracerebral hemorrhage (ICH), cephalohematoma, cord compression

Vacuum Extraction

- traction instrument used as alternative to forceps delivery; aids maternal pushing

Advantages

- easier to apply
- less anesthesia required
- less maternal soft-tissue injury compared to forceps

Disadvantages

- contraindicated if fetus at risk for coagulation defect
- suitable only for vertex presentations
- maternal pushing required
- contraindicated in preterm delivery
- EFW must be ≥ 2500 g
- vacuum can lose suction and dislodge, especially if CPD present (note that conversely, on occasion vacuums can be used to overcome CPD and achieve vaginal birth)

Specific Complications of Vacuum Extraction for Fetus

- increased incidence of cephalohematoma and retinal hemorrhages compared to forceps
- subglial hemorrhage, subaponeurotic hemorrhage, soft tissue trauma

**Limits for Trial of Vacuum**

- Any combination of 3 pulls and/or pop-offs
- 20 minutes with no delivery

Lacerations

- **first degree:** involves skin and vaginal mucosa but not underlying fascia and muscle
- **second degree:** involves fascia and muscles of the perineal body but not the anal sphincter
- **third degree:** involves the anal sphincter but does not extend through it
- **fourth degree:** extends through the anal sphincter into the rectal mucosa

Episiotomy**Definition**

- incision in the perineal body at the time of delivery
 - essentially a controlled second degree laceration
- **midline:** incision through central tendinous portion of perineal body and insertions of superficial transverse perineal and bulbocavernosus muscle
 - better healing but increased risk of deep tear
- **mediolateral:** incision through bulbocavernosus, superficial transverse perineal muscle, and levator ani
 - reduced risk of extensive tear but poorer healing and more pain
- easier to repair

Indications

- to reduce chance of third or fourth degree tear
- to relieve obstruction of the unyielding perineum
- instrumental delivery
- controversy over whether it is preferable to make a cut or let the perineum tear as needed
 - current evidence suggests letting perineum tear and then repair as needed (restricted use)

Complications

- infection, hematoma, extension into anal musculature or rectal mucosa, fistula formation

Restrictive vs. Routine Episiotomies with Vaginal Births

Episiotomy for vaginal birth. *Cochrane Database of Systematic Reviews* 2009; Issue 1

Study: This systematic review and meta-analysis of 8 RCTs assessed the effects of restrictive (only done for fetal indications or if severe perineal trauma was judged to be imminent) and routine (liberally done to prevent any tear) use of episiotomy during vaginal birth.

Patients: Of the 2709 patients in the routine episiotomy group, 2035 (75%) women had episiotomies. In the restrictive episiotomy group, 776 (28%) of the 2733 women had episiotomies.

Results: Restrictive episiotomies appear to have less severe perineal trauma (RR 0.67), less suturing (RR 0.71), and fewer healing complications at 7 days (RR 0.69) compared to routine episiotomies. There is no difference for pain measures, dyspareunia, urinary incontinence, and severe vaginal or perineal trauma, but there was an increased risk of anterior perineal trauma (RR 1.84) with restrictive episiotomy. Similar results were obtained when comparing restrictive versus routine mediolateral versus midline episiotomy.

Conclusions: Compared to routine use, restrictive use of episiotomy during vaginal delivery appears to be more beneficial.

Caesarean Delivery**Epidemiology**

- incidence 20-25%

Indications

- maternal: obstruction, active herpetic lesion on vulva, invasive cervical cancer, previous uterine surgery, underlying maternal illness (eclampsia, HELLP syndrome, heart disease)
- maternal-fetal: failure to progress, placental abruption or previa, vasa previa
- fetal: abnormal fetal heart tracing, malpresentation, cord prolapse, certain congenital anomalies

Types of Caesarean Incisions

- skin
 - vertical midline
 - ♦ rapid peritoneal entry and increased exposure
 - ♦ increased dehiscence
 - transverse
 - ♦ decreased exposure and slower entry
 - ♦ improved strength and cosmesis
- uterine
 - low transverse (most common) – in noncontractile segment – decreased chance for rupture in subsequent pregnancies
 - low vertical – used for very preterm infants, poorly developed maternal lower uterine segment
 - classical (rare) – in thick, contractile segment – used for transverse lie, fetal anomaly, >2 fetuses, lower segment adhesions, obstructing fibroid

Risks/Complications

- anesthesia
- hemorrhage (average blood loss ~1000 cc)
- infection (UTI, wound, endometritis)
- injury to surrounding structures (bowel, bladder, ureter, uterus)
 - single dose prophylactic antibiotic should be used (e.g. cefazolin 1-2 g)
- thromboembolism
- increased recovery time/hospital stay
- maternal mortality (<0.1%)

Puerperal Complications

- puerperium: 6-week period of adjustment after pregnancy when pregnancy-induced anatomic and physiologic changes are reversed



Postpartum Hemorrhage (PPH)

Definition

- loss of >500 mL of blood at the time of vaginal delivery, or >1000 mL with C/S
- early – within first 24h postpartum
- late – after 24h but within first 6 weeks

Epidemiology

- incidence 5-15%

Etiology (4 T's)

1. Tone

- uterine atony
 - ♦ most common cause of PPH
 - ♦ avoid by giving oxytocin with delivery of the anterior shoulder or placenta
 - ♦ occurs within first 24 hours
- due to:
 - ♦ labour (prolonged, precipitous, induced, augmented)
 - ♦ uterus (infection, over-distention)
 - ♦ placenta (abruption, previa)
 - ♦ maternal factors (grand multiparity, gestational HTN)
 - ♦ halothane anesthesia

2. Tissue

- retained placental products
- retained blood clots in an atonic uterus
- gestational trophoblastic neoplasia

3. Trauma

- laceration (vagina, cervix, uterus), episiotomy, hematoma (vaginal, vulvar, retroperitoneal), uterine rupture, uterine inversion

4. Thrombin

- coagulopathy
 - ♦ most identified prior to delivery (low platelets increases risk)
 - ♦ includes hemophilia, DIC, aspirin use, ITP, TTP, vWD (most common)
 - ♦ therapeutic anti-coagulation

Investigations

- assess degree of blood loss and shock by clinical exam
- explore uterus and lower genital tract for evidence of tone, tissue or trauma
- may be helpful to observe red-topped tube of blood – no clot in 7-10 minutes indicates coagulation problem

Management

- ABCs
- 2 large bore IVs and crystalloids
- CBC, coagulation profile, cross and type 4 units pRBCs
- treat underlying cause

Medical Therapy

- oxytocin 20 U/L NS or RL IV continuous infusion
 - in addition can give 10 U intramyometrial (IMM) after delivery of the placenta
- methylergonavine maleate (ergotamine) 0.25 mg IM/IMM q5min up to 1.25 mg; can be given as IV bolus of 0.125 mg (may exacerbate HTN)
- carboprost (Hemabate®) (synthetic PGF-2 alpha analog) 0.25 mg IM/IMM q15 min to max 2 mg (major prostaglandin side effects and contraindicated in cardiovascular, pulmonary, renal and hepatic dysfunction)

Local Control

- bimanual compression: elevate the uterus and massage through patient's abdomen
- uterine packing (mesh with antibiotic treatment)
- intrauterine Senstaken-Blakemore catheter for balloon tamponade – may slow hemorrhage enough to allow time for correction of coagulopathy or for preparation of an OR



Uterine atony is the most common cause of PPH.



DDx of Early PPH – 4 T's

1. Tone (atony)
2. Tissue (retained placenta, clots)
3. Trauma (laceration, inversion)
4. Thrombin (coagulopathy)

DDx of Late PPH

1. Retained products
2. ± endometritis
3. Sub-involution of uterus

Surgical Therapy (Intractable PPH)

- D&C (beware of vigorous scraping which may cause Asherman's syndrome)
- laparotomy with bilateral ligation of uterine artery (may be effective), internal iliac artery (not proven), ovarian artery, or hypogastric artery
- hysterectomy (last option) with angiographic embolization if post-hysterectomy bleeding

RETAINED PLACENTA**Definition**

- placenta undelivered after 30 minutes postpartum

Etiology

- placenta separated but not delivered
- abnormal placental implantation (placenta accreta, placenta increta, placenta percreta)

Risk Factors

- placenta previa, prior C/S, post-pregnancy curettage, prior manual placental removal, uterine infection

Clinical Features

- incomplete placenta removed
- risk of postpartum hemorrhage and infection

Investigations

- explore uterus
- assess degree of blood loss

Management

- 2 large bore IVs, type and screen
- Brant maneuver (firm traction on umbilical cord with one hand applying suprapubic pressure to avoid uterine inversion by holding uterus in place)
- oxytocin 10 IU in 20 mL NS into umbilical vein
- manual removal if above fails
- D&C if required

UTERINE INVERSION**Definition**

- turning inside out (inversion) of the uterus through cervix \pm vaginal introitus

Etiology/Epidemiology

- often iatrogenic (excess cord traction with fundal placenta)
- excessive use of uterine tocolytics
- more common in grand multiparous (lax uterine ligaments)
- 1/1500-1/2000 deliveries

Clinical Features

- can cause profound vasovagal response with vasodilation and hypovolemic shock
- shock may be disproportionate to maternal blood loss

Management

- urgent management essential, call anesthesia
- ABCs – initiate IV crystalloids
- can use tocolytic drug (e.g. terbutaline) or nitroglycerin IV to relax uterus and aid replacement
- replace uterus without removing placenta
- remove placenta manually and withdraw slowly
- IV oxytocin infusion (only after uterus replaced)
- re-explore uterus
- may require GA \pm laparotomy

**Etiology of Post-Partum Pyrexia****B-5W****Breast:** engorgement, mastitis**Wind:** atelectasis, pneumonia**Water:** UTI**Wound:** episiotomy, C/S site infection**Walking:** DVT, thrombophlebitis**Womb:** endometritis

Postpartum Pyrexia

Definition

- fever $>38^{\circ}\text{C}$ on any 2 of the first 10 days postpartum, except the first day

Etiology

- Wind** (atelectasis, pneumonia), **Water** (UTI), **Wound** (C/S incision or episiotomy site), **Walking** (pelvic thrombophlebitis, DVT), **Breast** (engorgement, mastitis – *S. aureus*), **Womb** (endometritis)

Investigations

- detailed history and physical exam, relevant cultures
- for endometritis: blood and genital cultures

Treatment

- depends on etiology
 - infection: empiric antibiotics, adjust when sensitivities available
 - endometritis/wound infection: clindamycin + gentamycin IV
 - mastitis: penicillin or cephalosporin
 - DVT: anticoagulants
- prophylaxis against post-C/S endometritis: begin antibiotic immediately after cord clamping and administer only 1-3 doses – cefazolin is most common choice

**Risk Factors for Endometritis**

C-section, intrapartum chorioamnionitis, prolonged labour, prolonged ROM, multiple vaginal examinations

ENDOMETRITIS

- definition: infection of uterine myometrium and parametrium
- clinical features: fever, chills, abdominal pain, uterine tenderness, foul-smelling discharge or lochia
- treatment: depends on infection severity; oral antibiotics if well, IV with hospitalization in moderate to severe cases

VENOUS THROMBOEMBOLISM

- see OB20



Mastitis

- definition: inflammation of mammary glands
- must rule out inflammatory carcinoma, as indicated
- differentiate from mammary duct ectasia – mammary duct(s) beneath nipple clogged and dilated \pm ductal inflammation \pm nipple discharge (thick, grey to green), often postmenopausal women

Table 21. Lactational versus Non-Lactational Mastitis

	Lactational	Non-Lactational
Epidemiology	More common than non-lactational Often 2-3 wks postpartum	Periductal mastitis most common Mean age 32 y
Etiology	<i>S. aureus</i>	May be sterile May be infected with <i>S. aureus</i> or other anaerobes Smoking is risk factor May be associated with mammary duct ectasia
Symptoms	Unilateral localized pain Tenderness Erythema	Subareolar pain May have subareolar mass Discharge (variable colour) Nipple inversion
Treatment	Heat or ice packs Continued nursing/pumping Antibiotics (dicloxacillin/cephalexin) (Erythromycin if pen-allergic)	Broad-spectrum antibiotics and I&D Total duct excision (definitive)
Abscess	Fluctuant mass Purulent nipple discharge Fever, leukocytosis D/c nursing, IV antibiotics (nafcillin/oxacillin), I&D usually required	If mass does not resolve, FNA to exclude cancer and U/S to assess presence of abscess Treatment includes antibiotics, aspiration or I&D (tends to recur) May develop mammary duct fistula A minority of non-lactational abscesses may occur peripherally in breast with no associated periductal mastitis (usually <i>S. aureus</i>)

Postpartum Mood Alterations

POSTPARTUM BLUES

- 85% of new mothers, onset day 3-10; extension of the “normal” hormonal changes and adjustment to a new baby
- self-limited, should resolve by 2 weeks
- manifested by mood lability, depressed affect, increased sensitivity to criticism, tearfulness, fatigue, irritability, poor concentration/despondency

POSTPARTUM DEPRESSION (PPD)

- definition: major depression occurring in a woman within 6 months of childbirth (see Psychiatry, PS10)
- epidemiology: 10-20%, risk of recurrence 50%
- risk factors
 - personal or family history of depression (including PPD)
 - prenatal depression or anxiety
 - stressful life situation
 - poor support system
 - unwanted pregnancy
 - colicky or sick infant
- clinical features: suspect if the “blues” last beyond 2 weeks, or if the symptoms in the first two weeks are severe (e.g. extreme disinterest in the baby, suicidal or homicidal/infanticide ideation)
- assessment: Edinburgh Postnatal Depression Scale or other
- treatment: antidepressants, psychotherapy, supportive care, ECT if refractory
- prognosis: interferes with bonding and attachment between mother and baby so it can have long term effects

POSTPARTUM PSYCHOSIS

- definition: onset of psychotic symptoms over 24-72 hours within first month postpartum, can present in the context of depression
- epidemiology: rare (0.2%)

Postpartum Care

Postpartum Office Visit at 6 Weeks

Care of Baby

- assess weight, feeding, immunization
- encourage breastfeeding if no contraindications

Care of Mother (The 10 Bs)

- **B**e careful: do not use douches or tampons for 4-6 weeks post-delivery
- **B**e fit: encourage gradual increases in walking, Kegel exercises
- **B**irth control: assess for use of contraceptives; breastfeeding is NOT an effective method of birth control
- **B**ladder: assess for urinary incontinence, maintain high fluid intake
- **B**leeding: (see *Lacerations*, OB47), 300 µg of RhIG should be given if Rh+ fetus and Rh- mother or extensive bleeding at delivery
- **B**lood pressure: especially if gestational HTN
- **B**lood tests: glucose, CBC (for anemia as sign of hematomas, retained placenta)
- **B**lues: see *Postpartum Mood Alterations*, OB51
- **B**owel: fluids and high-fibre foods, bulk laxatives; for hemorrhoids/perineal tenderness: pain meds, doughnut cushion, Sitz baths, ice compresses
- **B**reast and pelvic exam: watch for *Staphylococcal* or *Streptococcal* mastitis/abscess, ± Pap smear at 6 weeks

Physiological Changes Postpartum

- uterus weight rapidly diminishes through catabolism, cervix loses its elasticity and regains firmness
 - should involute ~1 cm below umbilicus per day in first 4-5 days, reaches non-pregnant state in 4-6 weeks postpartum
- ovulation resumes in ~45 days for non-lactating women and within 3-6 months for lactating women
- lochia: normal vaginal discharge postpartum
 - decreases and changes in colour from red (lochia rubra; presence of erythrocytes) → yellow (lochia serosa) → white (lochia alba; residual leukorrhea) over 3-6 weeks
 - foul smelling lochia suggests endometritis



The acronym **"BUBBLES"** for what to ask about when rounding on postpartum care. Modify this for C/S or vaginal delivery

Baby care and breastfeeding (latch, amount)

Uterus – firm or boggy?

Bladder function – Voiding well? Dysuria?

Bowel function – Passing gas or stool? Constipated?

Lochia or discharge – Any blood?

Episiotomy/laceration/incision – Pain controlled?

Symptoms of VTE – Dyspnea? Calf pain?

Breastfeeding Problems

- inadequate milk: consider domperidone
- breast engorgement: cool compress, manual expression/pumping
- nipple pain: clean milk off nipple after feeds, moisture cream, topical steroid if needed
- mastitis: treat promptly (see OB50)
- inverted nipples: makes feeding difficult
- maternal medications: may require pediatric consultation (see OB54)

Bladder Dysfunction

- pelvic floor prolapse can occur after vaginal delivery
- stress or urge urinary incontinence common
- increased risk with instrumental delivery or prolonged second stage
- conservative management: pelvic floor retraining with Kegel exercises, vaginal cones or pessaries, lifestyle modifications (e.g. limit fluid, caffeine intake)
- surgical management: minimally invasive procedures (tension-free vaginal tape, transobturator tape, midurethral sling) (see Gynecology, GY34)

Puerperal Pain

- "after pains" common in first 3 days due to uterine contractions; encourage simple analgesia
- ice packs can be used on perineum if painful
- encourage regular analgesia and stool softener

Drug and Food Safety During Pregnancy and Breastfeeding

- most drugs cross the placenta to some extent
- very few drugs are teratogenic, but very few drugs have proven safety in pregnancy
- use any drug with caution and only if necessary

Antibiotics

- safest: ampicillin, cephalosporins
- erythromycin: maternal liver damage (acute fatty liver)
 - used only if contraindication to penicillin use
- tetracyclines: stain infant's teeth, may affect long bone development
- sulpha drugs: anti-folate properties, therefore theoretical risk in T1; risk of kernicterus in T3
- metronidazole: anti-metabolite, therefore theoretical risk in T1
- chloramphenicol: grey baby syndrome (fetal circulatory collapse 2° to toxic accumulation)
- fluoroquinolones: risk of cartilage damage (in dog and rat studies)

Other Medications and Substances

- analgesics: acetaminophen preferable to ASA or ibuprofen

Documented adverse effects, contraindicated:

- ACE inhibitors: fetal renal defects, IUGR, oligohydramnios
- tetracycline: see above
- retinoids (e.g. Accutane®): CNS, craniofacial, cardiac, and thymic anomalies
- DES (and other estrogenic or androgenic compounds): vaginal adenosis, adenocarcinoma, uterine malformation in females exposed to DES in utero
- misoprostol: Mobius syndrome (congenital facial paralysis with or without limb defects)

Documented adverse effects, weigh benefits vs. risks and consider medication change:

- anticonvulsants
 - phenytoin associated with fetal hydantoin syndrome in 5-10% (IUGR, mental retardation, facial dysmorphism, congenital anomalies)
 - valproate associated with oNTD in 1%
 - carbamazepine associated with oNTD in 1-2%
 - generally recommended to remain on the lowest dose anticonvulsant appropriate for their condition
- lithium: Ebstein's cardiac anomaly, goitre, hyponatremia
- warfarin: increased incidence of spontaneous abortion, stillbirth, prematurity, IUGR
 - fetal warfarin syndrome (nasal hypoplasia, epiphyseal stippling, optic atrophy, mental retardation, intracranial hemorrhage)



Drug Resources during Pregnancy and Breastfeeding

- Motherisk at the Hospital for Sick Children in Toronto: www.motherisk.org
- Hale, T. Medications and Mothers' Milk, 11th Edition. Pharmasoft Publishing, 2004.

Substances

- alcohol: increased incidence of abortion and stillbirth, congenital anomalies
 - fetal alcohol syndrome (growth retardation, CNS involvement and facial anomalies)
- cigarette smoke: decreased birth weight, placenta previa/abruption, spontaneous abortion, preterm labour, stillbirth
- cocaine: microcephaly, growth retardation, prematurity, MR

Immunizations**Intrapartum**

- administration is dependent on the risk of infection vs. risk of immunization complications
- safe: tetanus toxoid, diphtheria, influenza, hepatitis B
- avoid live vaccines (risk of placental and fetal infection): polio, measles/mumps/rubella, varicella
- contraindicated: rubella, oral typhoid

Postpartum

- rubella vaccine for all non-immune mothers
- hepatitis B vaccine should be given to infant within 12h of birth if maternal status unknown or positive – follow-up doses at 1 and 6 months

Food**Caffeine**

- diuretic and stimulant properties
- readily crosses placenta
- possible risk for miscarriage and fetal growth retardation at high doses (>200-300 mg/day); note some of this presumed risk may be due to confounders, such as cigarette smoking
- based on a meta-analysis, consumption should be limited to no more than 150 mg per day from all sources during pregnancy and lactation

Herbal Teas and Preparations

- not enough scientific information about the safety of various herbs and herbal products to recommend their general use during pregnancy and lactation
- some herbal teas can have toxic or pharmacological effects on the mother or fetus
- chamomiles have been reported to exhibit adverse effects on the uterus

Food Borne Illnesses

- microbiological contamination of food may occur through cross-contamination and/or improper food handling
 - listeriosis (*Listeria monocytogenes*) and toxoplasmosis (*Toxoplasma gondii*) are of concern during pregnancy
 - avoid consumption of raw meats, fish, poultry, raw eggs, and unpasteurized dairy products
 - wash all raw fruit and vegetables thoroughly
 - avoid soft cheeses and pates as they may be sources of *Listeria*
- chemical contamination of food
 - current guideline for mercury of 0.5 ppm in fish is considered protective for the general population, including pregnant women
 - Health Canada advises pregnant women to limit consumption of top predator fish such as shark, swordfish and fresh/frozen tuna (not canned tuna) to one meal per month

**Sources of Caffeine**

5 oz cup coffee: 40-180 mg
 5 oz brewed tea: 20-90 mg
 12 oz cola: 46 mg
 Red Bull®: 67 mg
 Dark chocolate bar: 10 mg
 8 oz hot chocolate: 5 mg

**Herbal Teas Considered Safe in Moderation (2-3 cups/day)**

Citrus peel
 Ginger
 Lemon balm
 Linden flower – not with prior cardiac condition
 Orange peel
 Rose hip

**Radiation in Pregnancy**

Necessary amount to cause miscarriage: >5 rads
Necessary amount to cause malformations: >20-30 rads

Radiation

- ionizing radiation exposure is considered teratogenic at high doses
 - if indicated for maternal health, should be done
- imaging not involving direct abdominal/pelvic high dosage is not associated with adverse effects
 - higher dosage to fetus: plain x-ray of lumbar spine/abdomen/pelvis, barium enema, CT abdomen, pelvis, lumbar spine
- most investigations involve minimal radiation exposure (see Table 22)
- radioactive isotopes of iodine are contraindicated
- no known adverse effects from U/S or MRI

Table 22. Approximate Fetal Doses from Common Diagnostic Procedures

Examination	Estimated Fetal Dose (rad)	Number of Exams Safe in Pregnancy
Plain Film		
Abdomen	0.245	20
Pelvis	0.040	125
Lumbar spine	0.359	13
Thoracic spine	0.009	555
Chest (2 views)	0.00007	71 429
CT		
Abdomen (10 slices)	2.600	1
Pelvis (1 slice with scout film)	0.250	20
Lumbar spine (5 slices)	3.500	1
Chest	0.2-0.6	20

Adapted from Valentin, 2000.

Breastfeeding and Drugs

**Breastfeeding: Contraindicated Drugs****BREAST**

Bromocriptine/Benzodiazepines
Radioactive isotopes/Rizatriptan
Ergotamine/Ethosuximide
Amiodarone/Amphetamines
Stimulant laxatives/Sex hormones
Tetracycline/Tretinoin

- safe
 - penicillins, aminoglycosides, cephalosporins
 - oral contraceptive use (low dose) – OCP will decrease quantity but not affect composition of breast milk
 - medroxyprogesterone acetate
- avoid
 - chloramphenicol (bone marrow suppression)
 - metronidazole (mutagenic in vitro)
 - sulphonamides (hemolysis with G6PD deficiency)
 - nitrofurantoin (hemolysis with G6PD deficiency)
 - tetracycline
 - lithium
 - anti-neoplastics and immunosuppressants
 - psychotropic drugs (relative)

Common Medications

Table 23. Common Medications

Drug Name (Brand Name)	Dosing Schedule	Indications/Comments
betamethasone valerate (Celestone®)	12 mg IM q24h x 2 doses	Enhancement of fetal pulmonary maturity for PTL
carboprost (Hemabate®)	0.25 mg IM/IMM q15min; max 2 mg	Treatment of uterine atony
dexamethasone	6 mg IM q12h x 4 doses	Enhancement of fetal pulmonary maturity for PTL
dinoprostone (Cervidil®: PGE ₂ impregnated thread)	10 mg PV (remove after 12h) max of 3 doses	Induction of labour Advantage: can remove if uterine hyperstimulation
doxylamine succinate (Diclectin®)	2 tabs qhs + 1 tab qAM + 1 tab qPM max of 8 tabs/day	Each tablet contains 10 mg doxylamine succinate with vitamin B ₆ Used for hyperemesis gravidarum
folic acid	0.4-1 mg PO OD x 1-3 mo preconception and T1 5 mg PO OD with past Hx of NTD	Prevention of oNTD
methotrexate	50 mg/m ² IM or 50 mg po x 1 dose	For ectopic pregnancy or medical abortion
methylergonavine maleate (Ergotamine®)	0.25 mg IM/IMM q5min up to 1.25 mg or IV bolus 0.125 mg	Treatment of uterine atony
misoprostol (Cytotec®)	800-1000 µg PR x 1 dose 400 µg PO x 1 dose or 800 µg PV x 1 dose, 3 to 7 days after methotrexate	For treatment of PPH For medical abortion Also used for NSAID-induced ulcers (warn patients of contraindications)
oxytocin (Pitocin®)	0.5-2.0 mU/min IV, or 10 U/L N/S incr. by 1-2 mU/min q20-60min max of 36-48 mU/min 10 U IM at delivery of anterior shoulder and of placenta 20 U/L NS or RL IV continuous infusion	Augmentation of labour (also induction of labour) Prevention of uterine atony Treatment of uterine atony
PGE ₂ gel (Prostin® gel)	0.5 mg PV q6-12h; max of 3 doses	Induction of labour
Rh IgG (Rhogam®)	300 µg IM x 1 dose	Given to Rh negative women <ul style="list-style-type: none"> • Routinely at 28 wks GA • Within 72 hrs of birth of Rh +ve fetus positive • Positive Kleihauer-Betke test • With any invasive procedure in pregnancy • Ectopic pregnancy • Antepartum hemorrhage • Miscarriage or TA (dose: 50 µg IM only)



Misoprostol (Cytotec®) is also indicated to protect against NSAID-induced gastric ulcers in non-pregnant individuals. The use of misoprostol for cytoprotection is contraindicated in pregnancy. Warn female patients of this contraindication.



Common Discharge Medications
Oxycodone IR 5-10 mg po q4-6h PRN
Docusate sodium 100 mg PO BID

References

- American College of Obstetricians and Gynecologists www.acog.org
 The Society of Obstetricians and Gynaecologists of Canada www.sogc.org
 ABC of labour care: Care of the newborn in the delivery room. *BMJ* 1999; 318: 1403-1406.
 ABC of labour care: Obstetric emergencies. *BMJ* 1999; 318: 1342-1345.
 ABC of labour care: Operative delivery. *BMJ* 1999; 318: 1260-1264.
 ABC of labour care: Induction. *BMJ* 1999; 318: 995-998.
 ABC of labour care: Labour in special circumstances. *BMJ* 1999; 318: 1124-1127.
 ABC of labour care: Physiology and management of normal labour. *BMJ* 1999; 318: 793-796.
 ABC of labour care: Place of birth. *BMJ* 1999; 318: 721-723.
 ABC of labour care: Preterm labour and premature rupture of membranes. *BMJ* 1999; 318: 1059-1062.
 ABC of labour care: Relief of pain. *BMJ* 1999; 318: 927-930.
 ABC of labour care: Unusual presentations and positions and multiple pregnancy. *BMJ* 1999; 318: 1192-1194.
 Alfirevic Z. (2002). Oral misoprostol for induction of labour (Cochrane Review). The Cochrane Library, Issue 2.
 Antenatal Corticosteroid Therapy for Fetal Maturation. SOGC Clinical Practice Guidelines Policy Statement, December 1995: 53.
 Baskett, T. *Essential Management of Obstetric Emergencies*. 3rd ed. Clinical Press, Bristol, 1999.
 Bastian LA, Piscitelli JT. Is this patient pregnant? Can you reliably rule in or rule out early pregnancy by clinical examination? *JAMA*. 1997 Aug 20; 278(7): 586-91.
 Review
 Berghella V, et al. (2004). Cerclage for prevention of preterm birth in women with a short cervix found on transvaginal examination: A randomized trial. *Amer J Obs Gyn*. 191:1311-7.
 Boucher, M. Mode of Delivery for Pregnant Women infected by the Human Immunodeficiency Virus. SOGC Clinical Practice Guidelines. April 2001: 101.
 Boucher, M. and Gruslin, A. The Reproductive Care of Women living with Hepatitis C Infection. SOGC Clinical Practice Guidelines. October 2000: 96.
 Bricker L, Luckas M. (2002). Amniotomy alone for induction of labour (Cochrane Review). The Cochrane Library, Issue 2.
 Carol, Blenning. An Approach to the Postpartum Office Visit. *American Family Physician*. Dec 2005, 72(12); 2491 – 2496.
 Chodirker et al. Canadian Guidelines for Prenatal Diagnosis Part 1 & Part 2. SOGC Clinical Practice Guidelines. July 2001 and June 2000. No 105.
 Chyu JK, Strassner HT. Prostaglandin E2 for cervical ripening: a randomized comparison of cervidil vs. prepilid. *AMJ Obstet Gynecol* 1997. 177: 606-11.
 Crane, J. (2001). Induction of labour at term. SOGC Clinical Practice Guideline, 107:1-12.
 Fetal health Surveillance in Labour – Parts 1 and 2. SOGC Clinical Practical Guideline. January 1996, 45.
 Ford HB, Schust DJ. (2009) Recurrent Pregnancy Loss: Etiology, Diagnosis, and Therapy. *Rev Obstet Gynecol*. 2009 Spring; 2(2): 76–83.
 Gagnon A, and Wilson R. Obstetrical complications associated with abnormal maternal serum markers analytes. SOGC Clinical Practice Guidelines. Oct 2008, No 216; 918-932.
 Guidelines for exercise in pregnancy. SOGC Clinical Practical Guidelines. Committee Opinion. June 2003.
 Guidelines for the Management of Nausea and Vomiting in Pregnancy. SOGC Clinical Practice Guidelines Committee Opinion. November 1995: 12.
 Goldenberg et al. Epidemiology and causes of preterm birth. *The Lancet*. Jan 2008, Vol 371; 75 – 84.
 Guise JM, Berlin M, McDonagh M, Osterweil P, Chan B, Helfand M. Safety of vaginal birth after caesarean: a systematic review. *Obstet Gynec*. 2004 Mar; 103(3):420-9.
 Hannah, M. Post-term Pregnancy. SOGC Clinical Practice Guidelines Committee Opinion. March 1997: 15.
 Healthy Beginnings: Guidelines for Care during Pregnancy and Childbirth. SOGC Clinical Practice Guidelines Policy Statement. December 1998: 71.
 Hennessey MH, Rayburn WF, Stewart JD, Likes EC. Preeclampsia and induction of labour: a randomized comparison of prostaglandin E2 as an intracervical gel, with oxytocin immediately, or as a sustained – release vaginal insert. *AMJ Obstet Gynecol*. 1998. 179(5): 1204-9.
 Hod M, Bar J, Peled Y, Fried S, Katz I, Itzhak M, Ashkenazi S, Schindel B, Ben-Rafael Z. Antepartum management protocol. Timing and mode of delivery in gestational diabetes. *Obstet Gynecol*. 2009 Jan;113(1):206-17.
 Howarth GR, Botha DJ. (2002). Amniotomy plus intravenous oxytocin for induction of labour (Cochrane Review). The Cochrane Library, Issue 2.
 Kelly AJ, Tan B. (2002). Intravenous oxytocin alone for cervical ripening and induction of labour (Cochrane Review). The Cochrane Library, Issue 2.
 Kent, N. Prevention and Treatment of Venous Thromboembolism (VTE) in Obstetrics. SOGC Clinical Practice Guidelines. September 2000: 95.
 Koren, G. Motherisk Update: Caffeine During Pregnancy? *Canadian Family Physician*. April 2000. 46 : 801-3.
 Kotaska et al. Vaginal Delivery of Breech Presentation. SOGC Clinical Practice Guidelines. June 2009. No. 226; 557 – 566.
 Langlois S, Ford J, and Chitayat D. Carrier Screening for Thalassemia and hemoglobinopathies in Canada. SOGC Technical Update. Oct 2008, No 217; 950-959.
 Langlois S, Wilson R. Carrier Screening for Genetic Disorders in Individuals of Ashkenazi Jewish Descent. SOGC Clinical Practice Guidelines. Apr 2006, No 177; 324-332.
 Ling, F. and Duff, P. *Obstetrics and Gynecology, Principles for practice*. USA: McGraw-Hill Companies, 2002.
 Luckas M, Bricker L. (2000). Intravenous prostaglandin for induction of labour (Cochrane Review). The Cochrane Library, Issue 2.
 Meltzer, S., Leiter, L., Daneman, D., Gerstein, HC., Lau, D., Ludwig S., Yale, JF, Zimman, B., Lillie, D. 1998 Clinical Practice Guidelines for the Management of Diabetes in Canada. *CMAJ*. 1998, 159 (B suppl): S1-29.
 Menezes EV, Yakoob MY, Soomro T, Haws RA, Darmstadt GL, Bhutta ZA. (2009) Reducing stillbirths: prevention and management of medical disorders and infections during pregnancy. *BMC Pregnancy Childbirth*. 2009; 9(Suppl 1): S4.
 Midmer D, Biringer A, Carroll JC, Reid AJ, Wilson L, Stewart D, Tate M, Chalmers B. A Reference Guide for Providers: The ALPHA Form – Antenatal Psychosocial Health Assessment Form, 2nd Edition. Toronto: University of Toronto, Faculty of Medicine, Department of Family and Community Medicine, 1996.
 Ministry of Health and Long Term Care and Canadian Medical Association. Antenatal Record 1. Ontario.
 Ministry of Health and Long Term Care and Canadian Medical Association. Antenatal Record 2. Ontario.
 Money, D and Dobson, S. The prevention of early-onset group B streptococcal disease. SOGC Clinical Practice Guidelines. September 2004.
 Lowder JL, Burrows LJ, Krohn MA, Weber AM. Risk factors for primary and subsequent anal sphincter lacerations: a comparison of cohorts by parity and prior mode of delivery. *Am J Obstet Gynecol*. 2007 Apr;196(4):344.e1-5.
 Mount Sinai Hospital. First Trimester Combined Screening Program. 2001.
 North York General Hospital Genetics Program. Integrated Prenatal Screening. 1999.
 Ottinier WS, Menara MK, Brost BC. A randomized control trial of prostaglandin E2 intracervical gel and a slow release vaginal for preinduction cervical ripening. *AMJ Obstet Gynecol*. 1998. 179(2): 349-53.
 Schuurmans, N., MacKinnon, C., Lane C., Etches, D. Prevention and Management of Postpartum Hemorrhage. SOGC Clinical Practice Guidelines. April 2000: 88.
 SOGC. Fetal Health Surveillance: Antepartum and Intrapartum Consensus Guideline, Sept. 2007.
 SOGC. Conservative Management of Urinary Incontinence, No. 186. Dec 2006.
 SOGC. Midurethral Minimally Invasive Sling Procedures for Stress Urinary Incontinence. No 213. Aug 2008.
 Statistics Canada. 2005. Induced Abortion Statistics, 82-223-XWE, page 16 of 32.
 Stewart, D. A broader context for maternal mortality. *CMAJ*, Jan 31 2006, 174 (3); 302 – 303.
 Stewart JD, Rayburn WF, Farmer KC, Ciles EM, Schipaul AH Jr, Stanley JR. Effectiveness of prostaglandin E2 intracervical gel (prepidil) with immediate oxytocin vs. vaginal insert (cervidil) for induction of labour. *AMJ Obstet Gynecol* 1998. 179: 1175-80.
 Summers A, Langlois S, Wyatt P, Wilson D. Prenatal Screening for Fetal Aneuploidy. SOGC Clinical Practice Guidelines. Feb 2007, No 187; 146-161.
 Van den Hof, M. and Crane, J. Ultrasound Cervical Assessment in Predicting Preterm Birth. SOGC Clinical Practice Guidelines. May 2001: 102.

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Basic Anatomy Review

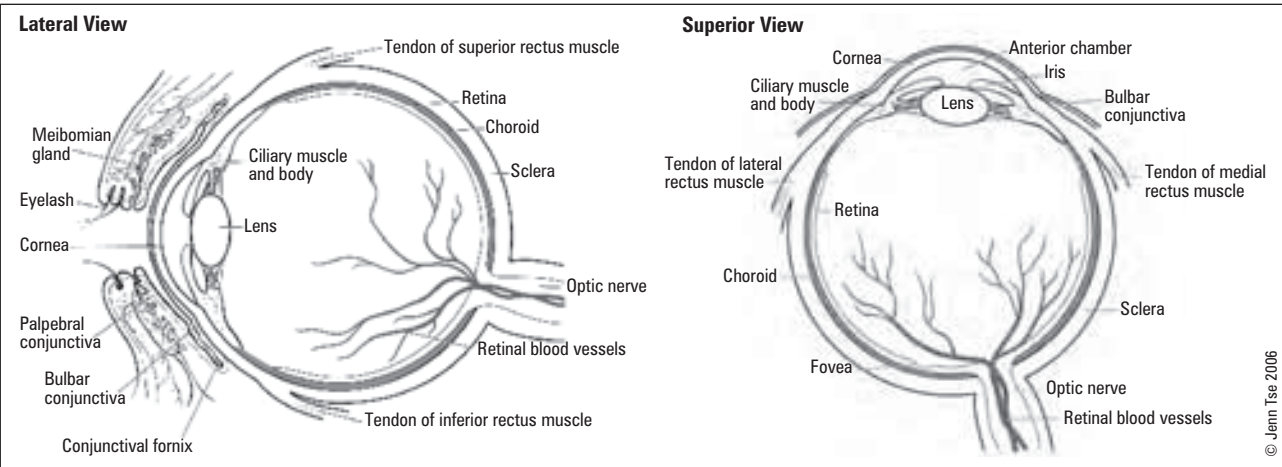


Figure 1. Anatomy of the Eye

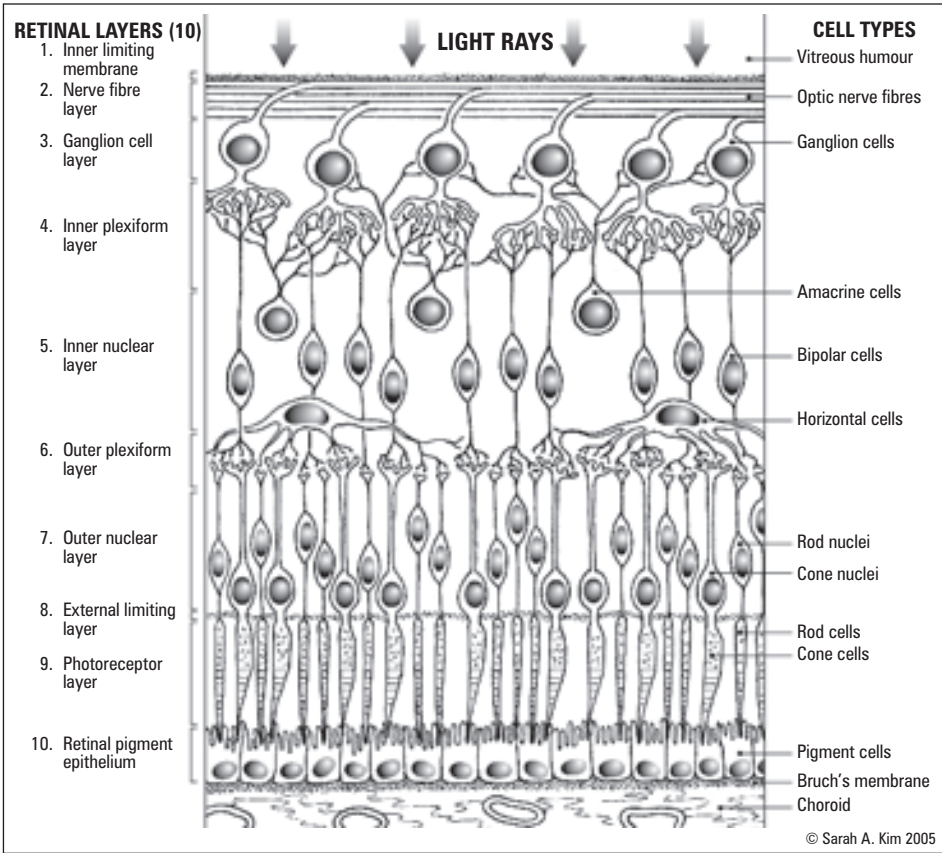


Figure 2. Layers of the Retina

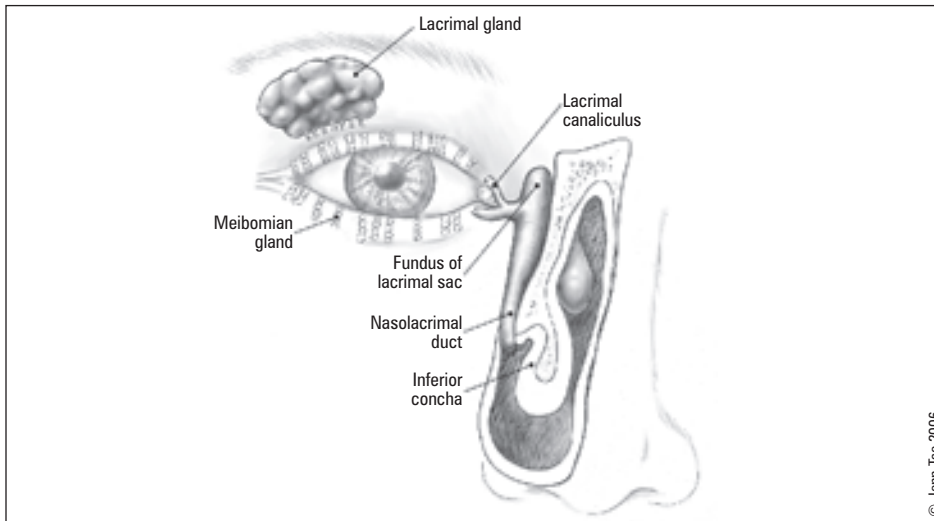


Figure 3. Tear Drainage from the Eye (Lacrimal Apparatus)

Differential Diagnoses of Common Presentations

Loss of Vision

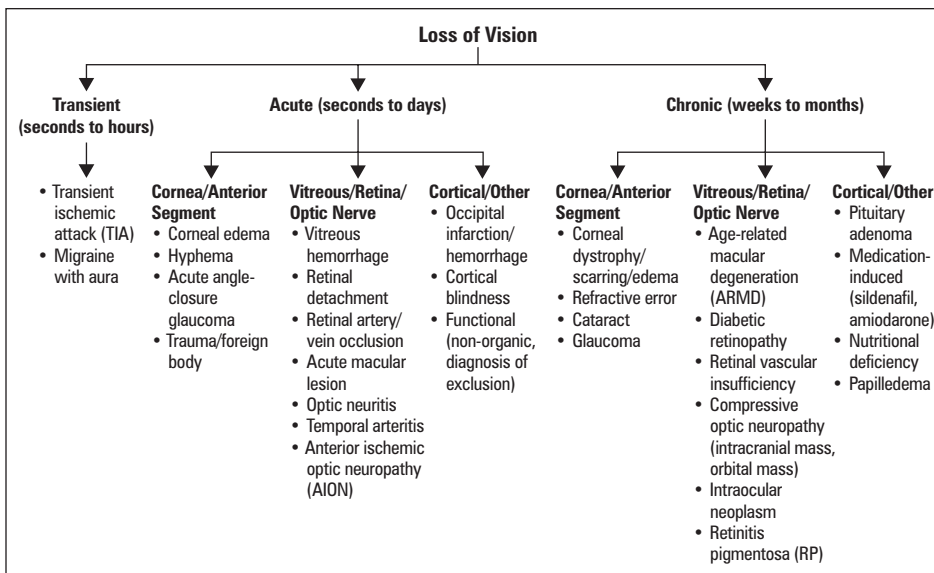


Figure 4. Loss of Vision

Red Eye

- lids/orbit/lacrimal system
 - hordeolum/chalazion
 - blepharitis
 - foreign body/laceration
 - dacryocystitis/dacryoadenitis
- conjunctiva/sclera
 - subconjunctival hemorrhage
 - conjunctivitis
 - dry eyes
 - pterygium
 - episcleritis/scleritis
 - preseptal/orbital cellulitis
- cornea
 - foreign body
 - keratitis
 - abrasion, laceration
 - ulcer



Top 3 in DDx of Acute Loss of Vision

1. Trauma/foreign body
2. Retinal artery/vein occlusion
3. Retinal detachment



Top 3 in DDx of Chronic Loss of Vision

Reversible

1. Cataract
2. Refractive error
3. Corneal dystrophy

Irreversible

1. Age-related macular degeneration
2. Glaucoma
3. Diabetic retinopathy

- anterior chamber
 - uveitis (iritis, iridocyclitis)
 - acute angle-closure glaucoma
 - hyphema
 - hypopyon
- endophthalmitis

Table 1. Common Differential Diagnosis of Red Eye

	Conjunctivitis	Acute Iritis	Acute Angle Closure Glaucoma	Keratitis
Discharge	Bacteria: purulent Virus: serous Allergy: mucous	No	No	Profuse tearing
Pain	No	++ (tender globe)	+++ (nauseating)	++ (on blinking)
Photophobia	No	+++	+	++
Blurred Vision	No	++	+++	Varies
Pupil	Normal	Smaller	Fixed in mid-dilation	Same or smaller
Injection	Conjunctiva with limbal pallor	Ciliary flush	Diffuse	Diffuse
Cornea	Normal or opacified	Keratic precipitates	Steamy	Infiltrate, edema, epithelial defects
Intraocular pressure	Normal	Varies	Increased markedly	Normal or increased
Anterior chamber	Normal	Cells + flare	Shallow	Cells + flare or normal
Other	Large, tender pre-auricular (auricular) node if viral	Posterior synechiae	Coloured halos Nausea and vomiting	



Not every red eye has conjunctivitis.

Ocular Pain

- differentiate from ocular ache: eye fatigue (asthenopia)
- herpes zoster prodrome
- trauma/foreign body
- keratitis
- corneal abrasion, corneal ulcer
- acute angle-closure glaucoma
- acute uveitis
- scleritis, episcleritis
- optic neuritis
- ocular migraine

Floaters

- vitreous syneresis (shrinkage and collapse of vitreous gel)
- posterior vitreous detachment (PVD)
- vitreous hemorrhage
- retinal tear/detachment
- posterior uveitis

Flashes of Light (Photopsia)

- posterior vitreous detachment (PVD)
- retinal tear/detachment
- migraine with aura

Photophobia (Severe Light Sensitivity)

- corneal abrasion, corneal ulcer
- keratitis
- acute angle-closure glaucoma
- iritis
- meningitis, encephalitis
- migraine

Diplopia (Double Vision)

- binocular diplopia: strabismus, CN palsy (III, IV, VI) secondary to ischemia, diabetes, tumour, trauma, myasthenia gravis, muscle restriction/entrapment, thyroid ophthalmopathy, internuclear ophthalmoplegia (INO) 2° to multiple sclerosis, brainstem infarct
- monocular diplopia: refractive error, strands of mucus in tear film, keratoconus, cataracts, dislocated lens, peripheral iridotomy

Ocular Problems in the Elderly

- blepharitis
- ptosis
- entropion, ectropion
- dry eyes, epiphora (excessive tearing)
- presbyopia
- cataracts
- glaucoma
- age-related macular degeneration
- retinal artery/vein occlusion
- temporal arteritis (arteritic ischemic optic neuropathy)

Ocular Problems in the Contact Lens Wearer

- superficial punctate keratitis (SPK)/dry eyes
- solution hypersensitivity
- tight lens syndrome
- corneal abrasion
- giant papillary conjunctivitis
- sterile corneal infiltrates (immunologic)
- infected ulcers (*Pseudomonas*, *Acanthamoeba*)

Ocular Emergencies



These require urgent consultation to an ophthalmologist for management

Sight Threatening

- lid/globe lacerations
- corneal ulcer
- gonococcal conjunctivitis
- acute iritis
- acute angle-closure glaucoma
- central retinal artery occlusion (CRAO)
- intraocular foreign body
- retinal detachment (especially macula threatening)
- endophthalmitis

Life Threatening

- proptosis (rule out cavernous sinus fistula or thrombosis)
- CN III palsy with dilated pupil (intracranial aneurysm or neoplastic lesion)
- papilledema (must rule out intracranial mass lesion)
- orbital cellulitis
- giant cell (temporal) arteritis
- leukocoria – white pupil (must rule out retinoblastoma)

The Ocular Examination

Note: Sometimes vision may be blurry secondary to eye drops/ointment/mucus or applying too much pressure when patching. Encourage the patient to blink before starting the exam and wait until the patient's vision is clear before continuing.

VISION ASSESSMENT

- always test visual acuity first
- test best corrected visual acuity (BCVA) whenever possible (i.e. corrective lenses)
- test each eye individually, starting with the right eye, and covering the untested eye
- assess distance and near vision
- improvement with a pinhole indicates an uncorrected refractive error

Visual Acuity – Distance

- Snellen Fraction (Figure 5) = $\frac{\text{testing distance (usually 20 feet or 6 metres)}}{\text{smallest line patient can read on the chart}}$
- e.g. 20/40 = what the patient can see at 20 feet (numerator), a “normal” person can see at 40 feet (denominator)

Example 1

SC
V 20/40 -1
20/80 +2 → 20/25 PH

Example 2

CC
V CF 3'
HM

Note: RIGHT EYE visual acuity always listed on top.

V	Vision
SC	Without correction
CC	With correction
20/40 -1	All except one letter of 20/40
20/80 +2	All of 20/80 plus two letters of 20/70
PH	Visual acuity with pinhole correction
CF	Counting fingers
HM	Hand motion

Figure 5. Ophthalmology Nomenclature for Visual Acuity



- OD = oculus dexter = right eye
- OS = oculus sinister = left eye
- OU = oculus uterque = both eyes

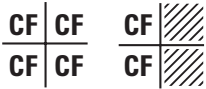


A Snellen visual acuity of 20/20 equates to "normal" vision.



Infant and Child Visual Acuity

- 6-12 months – 20/120
- 1-2 years – 20/80
- 2-4 years – 20/20



RIGHT EYE fields drawn on right side;
LEFT EYE fields drawn on left side
(as if seen through patient's eyes).

CF Able to count fingers in specified quadrant with peripheral vision

Gross visual field deficit in specified quadrant using peripheral vision

Figure 6. Ophthalmology
Nomenclature for Visual Fields by Confrontation



For patients with dark irises, test the pupils using an ophthalmoscope focused on the red reflex. This will provide a better view than using a penlight.



Changing fixation from distance to near results in the "near reflex":

1. Eye convergence
2. Pupil constriction
3. Lens accommodation

- testing hierarchy for low vision: Snellen acuity (20/x) → counting fingers at x distance (CF) → hand motion (HM) → light perception with projection (LP with projection) → light perception (LP) → no light perception (NLP)
- legal blindness is BCVA that is $\leq 20/200$ in the better eye, or a limit to the binocular central field of vision < 20 degrees
- minimum visual requirements to operate a non-commercial automobile in Ontario are: with both eyes open and examined together, 20/50 BCVA, a visual field of 120 continuous degrees along the horizontal meridian, and a visual field of 15 continuous degrees above and below fixation

Visual Acuity – Near

- use pocket vision chart (Rosenbaum Pocket Vision Screener)
- record Jaeger (J) or Point number and testing distance (usually 30 cm) e.g. J2 @ 30 cm
- conversion to distance visual acuity possible (e.g. immobile patient, no distance chart available)

Visual Acuity for Infants, Children, Non-English Speakers, and Dysphasics

- newborns
 - visual acuity cannot be tested
- 3 mos-3 yrs (can only assess visual function, not acuity)
 - test each eye for fixation using an interesting object
 - noted as "CSM" = central, steady and maintained
- 3 years until alphabet known
 - pictures or letter cards/charts such as the HOTV or Sheridan-Gardner test (children point to the optotypes on a provided matching card)
 - tumbling "E" chart

Colour Vision

- test with Ishihara pseudoisochromatic plates
- record number of correctly identified plates presented to each eye, specify incorrect plates
- important for testing optic nerve function (e.g. optic neuritis, chloroquine use, thyroid ophthalmopathy)
- note: red-green colour blindness is sex linked and occurs in 7-10% of males

VISUAL FIELDS

- test "visual fields by confrontation" (4 quadrants, each eye tested separately) for estimate of visual field loss (Figure 6)
- accurate, quantifiable assessment with automated visual field testing (Humphrey or Goldmann) or Tangent Screen
- use Amsler grid (each eye individually) to test for central or paracentral scotomas (island-like gaps in the vision), for patients with AMD

PUPILS

- use reduced room illumination with patient focusing on distant object to prevent "near reflex"
- examine pupils for shape, size, symmetry and reactivity to light (both direct and consensual response)
- test for relative afferent pupillary defect (RAPD) with swinging flashlight test
- test pupillary constriction portion of near reflex by bringing object close to patient's nose
- "normal" pupil testing often noted as "PERLA" = pupils equal, round, and reactive to light and accommodation

ANTERIOR CHAMBER DEPTH

- shine light tangentially from temporal side
- shallow anterior chamber: $> 2/3$ of nasal side of iris in shadow (Figure 9)

EXTRAOCULAR MUSCLES

Alignment

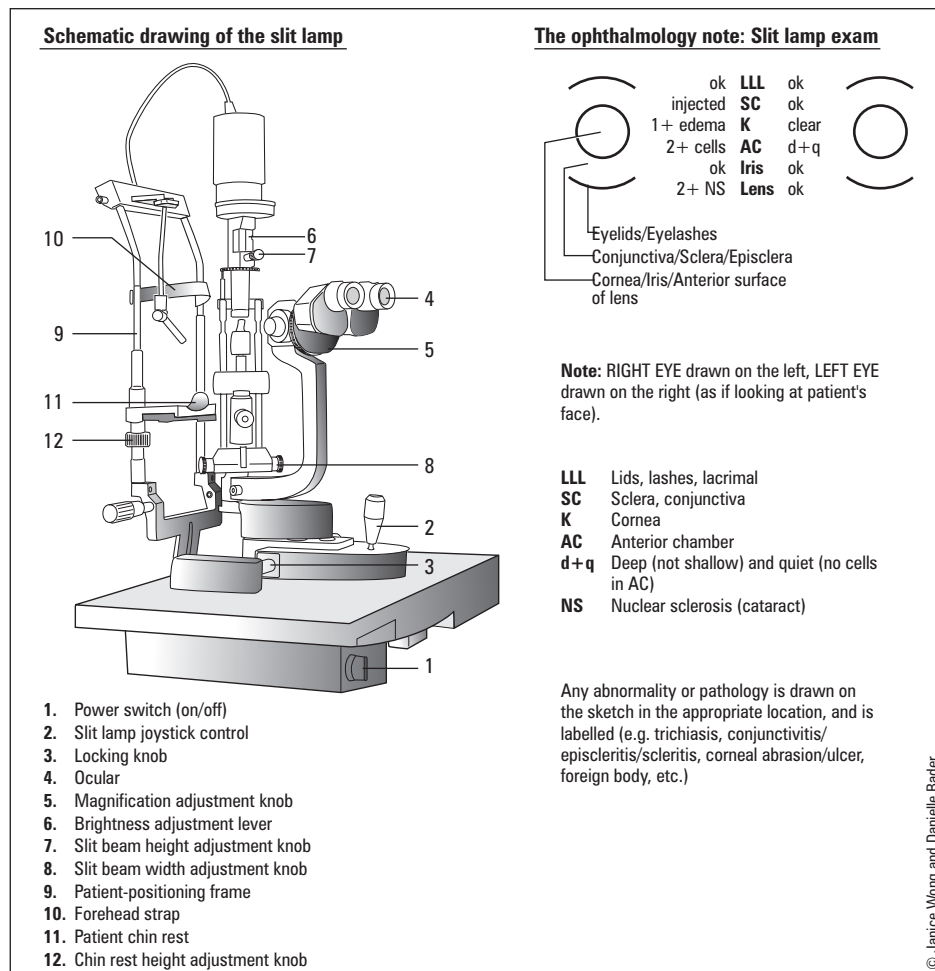
- Hirschberg corneal reflex test
 - examine in primary position of gaze (e.g. straight ahead) with patient focusing on distant object
 - shine light into patient's eyes from ~30 cm away
 - corneal light reflex should be symmetric and at the same position on each cornea
- strabismus testing as indicated (cover test, cover-uncover test, prism testing) (see *Strabismus*, OP38)

Movement

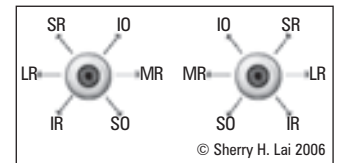
- examine movement of eyeball through six cardinal positions of gaze (Figure 8)
- ask patient if diplopia is present in any position of gaze
- observe for horizontal, vertical or rotatory nystagmus (rhythmic, oscillating movements of the eye)
- resolving horizontal nystagmus at end gaze is usually normal
- see side box for cranial nerve innervation of extraocular muscles

EXTERNAL EXAMINATION

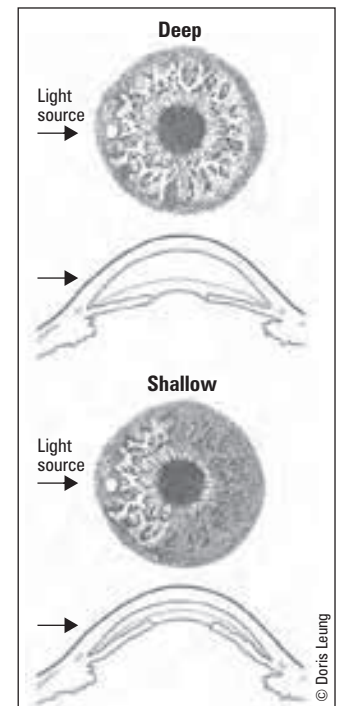
- the four Ls
 - lymph nodes (preauricular, submandibular)
 - lids
 - lashes
 - lacrimal system

SLIT-LAMP EXAMINATION**Figure 7. Slit-Lamp**

- systematically examine all structures of the anterior segment + anterior vitreous
 - lids (including upper lid eversion if necessary), lashes, and lacrimal system
 - conjunctiva and sclera
 - cornea
 - iris

**Figure 8. Diagnostic Positions of Gaze to Isolate Primary Action of Each Muscle**

- CN III – Superior, Medial and Inferior Rectus, Inferior Oblique
- CN IV – Superior Oblique (SO)
- CN VI – Lateral Rectus (LR)

**Figure 9. Estimation of Anterior Chamber Depth****Central Corneal Thickness**

Average CCT = 550 μ m
 A thick cornea overestimates IOP by GAT
 A thin cornea underestimates IOP by GAT

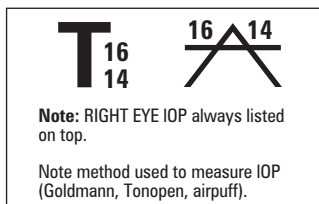


Figure 10. Tonometry

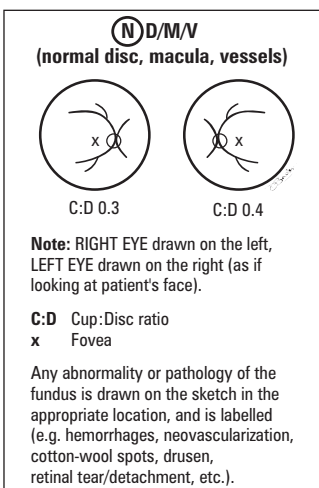
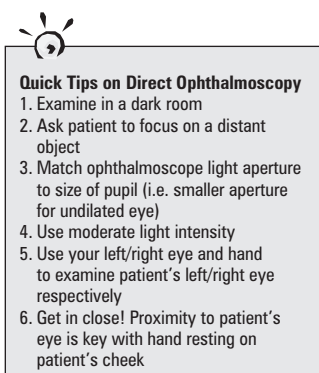
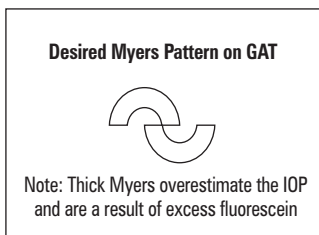
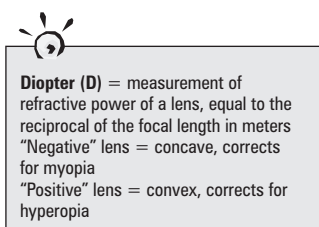
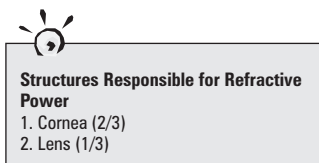


Figure 11. Fundus



- anterior chamber (for depth, cells and flare)
 - ♦ to observe cells and flare
 1. Dark room
 2. High power beam
 3. 1 mm beam height
 4. Thin beam
 5. Highest magnification
 6. Approach at angle and focus on anterior chamber (space between cornea and lens)
- lens
- anterior vitreous
- when necessary, use:
 - fluorescein dye – stains Bowman's membrane in de-epithelialized cornea; dye appears green with cobalt blue filter/red light
 - Rose Bengal dye – stains devitalized corneal epithelium
- special lenses (78 or 90 diopter) used with the slit-lamp allow a binocular, stereoscopic view of the fundus and vitreous

TONOMETRY

- measurement of intraocular pressure (IOP) (Figure 10)
- normal range is 10-21.5 mmHg (average 15 mmHg)
- commonly measured by:
 - Goldmann applanation tonometry (GAT) – gold standard, performed using the slit-lamp with special tip (prism)
 - Tonopen – benefit is portability and use of disposable probe tips. Use when cornea is scarred/asymmetric (GAT inaccurate)
 - air puff (non-contact and least reliable)
- use topical anesthetic for Goldmann and Tonopen

OPHTHALMOSCOPY/FUNDOSCOPY

- performed with:
 - direct ophthalmoscope (monocular with small field of view, only posterior pole visualized)
 - slit-lamp with 78 or 90 diopter lens (binocular view, visualization to mid-periphery of retina)
 - indirect ophthalmoscopy with headlamp and 20 or 28 diopter lens (binocular view, visualization of entire retina to ora serrata/edge of retina)
- best performed with pupils dilated (see Table 8 for list of mydriatics and cycloplegics)
- 1. assess red reflex
 - light reflected off the retina produces a "red reflex" when viewed from ~1 foot away
 - anything that interferes with the passage of light will diminish the red reflex (e.g. large vitreous hemorrhage, cataract)
- 2. examine the posterior segment of the eye (Figure 11)
 - vitreous
 - optic disc (colour, cup:disc ratio, sharpness of disc margin)
 - macula (~2 disc diameters temporal to disc), fovea (foveal light reflex)
 - retinal vessels
 - retinal background
- contraindications to pupillary dilatation
 - shallow anterior chamber – can precipitate acute angle-closure glaucoma
 - iris-supported anterior chamber lens implant
 - potential neurologic abnormality requiring pupil evaluation
 - use caution with cardiovascular disease – mydriatics may cause tachycardia

Optics

REFRACTION

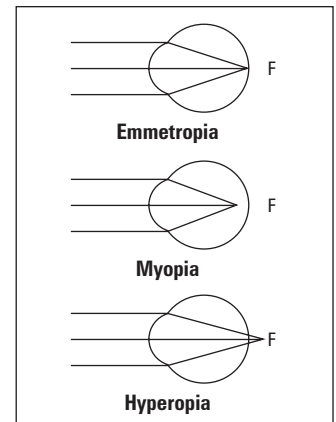
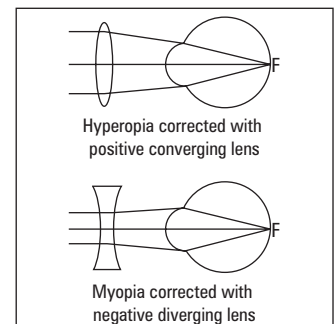
- two techniques used
 - Flash/Streak Retinoscopy – refractive error determined objectively by the examiner by use of lenses and retinoscope
 - Manifest – subjective trial using phoropter (device the patient looks through that is equipped with lenses)
- a typical lens prescription would contain:
 - sphere power in diopters (D), negative lens for myopes, positive lens for hyperopes
 - cylinder power (in D) to correct astigmatism (always positive value), axis of cylinder in degrees
 - "add" (bifocal/progressive reading lens) for presbyopes
 - e.g. -1.50 + 1.00 x 120 degrees, add +2.00

REFRACTIVE EYE SURGERY

- permanently alters corneal refractive properties by ablating tissue to change curvature of the cornea
- used for correction of myopia, hyperopia, and astigmatism
- common types include photorefractive keratectomy (PRK) and LASIK (see *Surgical Ophthalmology*, OP43)
- potential risks/side-effects: infection, undercorrection/overcorrection, decreased night vision, corneal haze, dry eyes, regression, complete sever of corneal flap (LASIK only)

Table 2. Optics

	Pathophysiology	Clinical Features	Treatment	Complications
Emmetropia	<ul style="list-style-type: none"> • Image of distant objects focus exactly on the retina (Figure 12) 	<ul style="list-style-type: none"> • No refractive error 		
Myopia	<ul style="list-style-type: none"> • Globe too long relative to refractive mechanisms, or refractive mechanisms too strong • Light rays from distant object focus in front of retina → blurring of (distance) vision (Figure 12) 	<ul style="list-style-type: none"> • "Nearsightedness" • Usually presents in 1st or 2nd decade, stabilizes in 2nd and 3rd decade; rarely begins after age 25 except in patients with diabetes or cataracts • Blurring of distance vision; near vision usually unaffected • Prevalence of 30-40% in U.S. population 	<ul style="list-style-type: none"> • Correct with negative diopter/concave/"negative" lenses to diverge light rays (Figure 13) • Refractive eye surgery 	<ul style="list-style-type: none"> • Retinal tear/detachment, macular hole, open angle glaucoma • Complications not prevented with refractive correction
Hyperopia	<ul style="list-style-type: none"> • Globe too short relative to refractive mechanisms, or refractive mechanisms too weak • Light rays from distant object focus behind retina → blurring of near ± distant vision (Figure 12) • May be developmental or due to any etiology that shortens globe 	<ul style="list-style-type: none"> • "Farsightedness" • Youth: usually do not require glasses (still have sufficient accommodative ability to focus image on retina), but may develop accommodative esotropia (see <i>Strabismus</i>, OP38) • 30s-40s: blurring of near vision due to decreased accommodation, may need reading glasses • >50s: blurring of distance vision due to severely decreased accommodation 	<ul style="list-style-type: none"> • When symptomatic, correct with positive Diopter/convex/"plus" lenses to converge light rays (Figure 13) • Refractive eye surgery 	<ul style="list-style-type: none"> • Angle-closure glaucoma, particularly later in life as lens enlarges
Astigmatism	<ul style="list-style-type: none"> • Light rays not refracted uniformly in all meridians due to non-spherical surface of corneas or non-spherical lens (e.g. football-shaped) • Two types: <ul style="list-style-type: none"> ▪ Regular – curvature uniformly different in meridians at right angles to each other ▪ Irregular – distorted cornea caused by injury, keratoconus (cone-shaped cornea), corneal scar, or severe dry eye 	<ul style="list-style-type: none"> • Affects approximately 30% of population, with prevalence increasing with age • Mild astigmatism unnoticeable • Higher amounts of astigmatism may cause blurry vision, squinting, asthenopia, or headaches 	<ul style="list-style-type: none"> • Correct with cylindrical lens (if regular), try contact lens (if irregular) • Refractive eye surgery 	
Presbyopia	<ul style="list-style-type: none"> • Normal aging process (>40 years) • Hardening/reduced deformability of the lens results in decreased accommodative ability • Accommodative power is 14D at age 10, diminishes to 3.5D by 40 • Near images cannot be focused onto the retina (focus is behind the retina as in hyperopia) 	<ul style="list-style-type: none"> • If initially emmetropic, person begins to hold reading material farther away, but distance vision remains unaffected • If initially myopic, person removes distance glasses to read • If initially hyperopic, symptoms of presbyopia occur earlier 	<ul style="list-style-type: none"> • Correct with positive diopter/convex/"plus" lenses for reading 	
Anisometropia	<ul style="list-style-type: none"> • Difference in refractive errors between eyes 			<ul style="list-style-type: none"> • Second most common cause of amblyopia in children

**Figure 12. Emmetropia and Refractive Errors****Figure 13. Correction of Refractive Errors**

The Orbit



Globe Displacement

Table 3. Exophthalmos (proptosis) and Enophthalmos

	Exophthalmos (proptosis)	Enophthalmos
Definition	<ul style="list-style-type: none"> Anterior displacement (protrusion) of the globe <ul style="list-style-type: none"> Exophthalmos generally refers to an endocrine etiology or protrusion of >18 mm (as measured by a Hertel exophthalmometer) Proptosis generally refers to other etiologies (e.g. cellulitis) or protrusion of <18 mm 	<ul style="list-style-type: none"> Posterior displacement (retraction) of the globe
Investigations	<ul style="list-style-type: none"> CT/MRI head/orbits, ultrasound orbits, thyroid function tests 	<ul style="list-style-type: none"> CT/MRI orbits
Etiology	<ul style="list-style-type: none"> Note: rule out pseudoexophthalmos (e.g. lid retraction) Graves' disease (unilateral or bilateral, most common cause in adults) Orbital cellulitis (unilateral, most common cause in children) Primary or secondary orbital tumours Orbital/retrobulbar hemorrhage Cavernous sinus thrombosis or fistula 	<ul style="list-style-type: none"> "Blow-out" fracture (see <i>Ocular Trauma</i>, OP42) Orbital fat atrophy Congenital abnormality Metastatic disease

Preseptal Cellulitis

- infection of soft tissue anterior to orbital septum

Etiology

- usually follows periorbital trauma or dermal infection

Clinical Features (Table 4)

- tender, swollen and erythematous lids
- ± low-grade fever
- NORMAL visual acuity, pupils, extraocular movements (EOM)
- NO exophthalmos or RAPD
- may lead to orbital cellulitis

Treatment

- warm compresses
- systemic antibiotics (suspect *H. influenzae* in children; *S. aureus* or *Streptococcus* in adults)
 - e.g. amoxilin-clavulanic acid
- if severe or child <1 year treat as orbital cellulitis



Orbital Cellulitis

- OCULAR and MEDICAL EMERGENCY**
- inflammation of orbital contents posterior to orbital septum
- common in children, elderly and immunocompromised

Etiology

- usually secondary to sinus/facial/tooth infections or trauma

Clinical Features (Table 4)

- decreased visual acuity, red eye
- pain with and without movement
- headache and fever
- lid erythema, tenderness, and edema with difficulty opening eye
- conjunctival injection and chemosis (conjunctival edema)
- proptosis, limitation of ocular movements (ophthalmoplegia)
- ± RAPD

Treatment

- admit, blood cultures x2, orbital CT, IV antibiotics (ceftriaxone + vancomycin) for 1 week
- surgical drainage of abscess with close follow-up, especially in children



Orbital cellulitis is life-threatening if untreated (mortality of 17-20% without antibiotic use). Prompt diagnosis and treatment is essential.

Complications

- optic nerve inflammation, cavernous sinus thrombosis, meningitis and brain abscess with possible loss of vision, death

Table 4. Differentiating Between Preseptal and Orbital Cellulitis

Finding	Preseptal Cellulitis	Orbital Cellulitis
Fever	May be present	Present
Lid edema	Moderate to severe	Severe
Chemosis	– or mild	Marked
Proptosis	–	+
Pain on eye movement	–	+
Ocular mobility	Normal	Decreased
Vision	Normal	Diminished ± diplopia
RAPD	Absent	May be seen
Leukocytosis	Moderate	Marked
ESR	Normal or elevated	Elevated
Additional findings	Skin infection	Sinusitis, dental abscess

Lacrimal Apparatus

- tear film made up of three layers
 - an outer oily layer (reduces evaporation): secreted by the Meibomian glands
 - a middle watery layer (forms the bulk of the tear film): constant secretion from conjunctival glands and reflex secretion by lacrimal gland with ocular irritation or emotion
 - an inner mucinous layer (aids with tear adherence to cornea): secreted by conjunctival goblet cells
- tears drain from the eyes through upper and lower lacrimal puncta → superior and inferior canaliculi → lacrimal sac → nasolacrimal duct → nasal cavity behind inferior concha (Figure 3)

Dry Eye Syndrome (Keratoconjunctivitis Sicca)

Etiology

- idiopathic – tear production normally decreases with aging
- blepharitis
- ectropion – downward and outward turning of lower eyelid
- decreased blinking (CN VII palsy)
- diminished corneal sensitivity (e.g. neurotrophic keratitis)
- systemic diseases: rheumatoid arthritis, Sjögren's syndrome, sarcoidosis, amyloidosis, leukemia, lymphoma
- medications: anticholinergics, diuretics, antihistamines, oral contraceptives
- vitamin A deficiency

Clinical Features

- dry eyes, red eyes, foreign body sensation, blurred vision, tearing
- slit-lamp exam: decreased tear meniscus, decreased tear break up time (TBUT, normally should be 10 seconds), superficial punctate keratitis (SPK)
- stains with fluorescein/Rose Bengal
- Schirmer's test: measures tear quantity on surface of eye in 5 minute time period (<10 mm of paper strip wetting in 5 minutes is considered a dry eye)

Complications

- erosions and scarring of cornea

Treatment

- medical: nonpreserved artificial tears up to q1h and ointment at bedtime (preservative toxicity becomes significant if used more than q4h)
- procedural: punctal occlusion (punctal plug insertion), lid taping, tarsorrhaphy (sew lids together) if severe
- treat underlying cause



Excessive tearing can be caused by dry eyes – if the tear quality is insufficient, “reflex tearing” may occur.

Epiphora (Excessive Tearing)

Etiology

- emotion
- environmental stressor (cold, wind, pollen, sleep deprivation)
- ectropion, entropion, trichiasis
- conjunctivitis
- corneal foreign body, keratitis
- dry eyes (reflex tearing)
- lacrimal drainage obstruction (aging, rhinitis, dacryocystitis, congenital failure of canalization)
- paradoxical lacrimation (crocodile tears)

Investigations

- using fluorescein dye, examine for punctal reflux by pressing on canaliculi
- Jones dye test – fluorescein placed in conjunctival cul-de-sac, and cotton applicator placed in nose to detect flow (i.e. rule out lacrimal drainage obstruction)

Treatment

- lid repair for ectropion or entropion
- eyelash removal for trichiasis
- punctal irrigation
- nasolacrimal duct probing (infants)
- tube placement: temporary (Crawford) or permanent (Jones)
- surgical: dacryocystorhinostomy (DCR) – forming a new connection between the lacrimal sac and the nasal cavity



Dacryocystitis

- acute or chronic infection of the lacrimal sac
- most commonly due to obstruction of the nasolacrimal duct
- commonly associated with *S. aureus*, *S. pneumoniae*, *Pseudomonas* species

Clinical Features

- pain, swelling, redness over lacrimal sac at medial canthus
- tearing, crusting, ± fever
- digital pressure on the lacrimal sac may extrude pus through the punctum
- in the chronic form, tearing may be the only symptom

Treatment

- warm compresses, nasal decongestants, systemic and topical antibiotics
- if chronic, obtain cultures by aspiration
- once infection resolves, consider dacryocystorhinostomy (see *Surgical Ophthalmology*, OP43)



Dacryoadenitis

- inflammation of the lacrimal gland (outer third of upper eyelid)
- acute causes: *S. aureus*, mumps, EBV, herpes zoster, *N. gonorrhoeae*
- chronic causes: lymphoma, leukemia, sarcoidosis, tuberculosis, thyroid ophthalmopathy

Clinical Features

- pain, swelling, tearing, discharge, redness of the outer region of the upper eyelid
- chronic form is more common and may present as painless enlargement of the lacrimal gland

Treatment

- supportive: warm compresses, oral NSAIDs
- systemic antibiotics if bacterial cause
- if chronic, treat underlying disorder

Lids and Lashes

Lid Swelling

Etiology

- commonly due to allergy, with shrivelling of skin between episodes
- dependent edema on awakening (e.g. CHF, renal or hepatic failure)
- orbital venous congestion due to mass or cavernous sinus fistula
- dermatochalasis (loose skin due to aging or heredity)
- lid cellulitis, thyroid disease (e.g. myxedema), trauma, chemosis

Ptosis

- drooping of upper eyelid

Etiology

- aponeurotic: disinsertion or dehiscence of levator aponeurosis (most common)
 - associated with advancing age, trauma, surgery, pregnancy, chronic lid swelling
- mechanical
 - incomplete opening of eyelid due to mass or scarring
- neuromuscular
 - myasthenia gravis (neuromuscular palsy), myotonic dystrophy
 - CN III palsy
 - Horner's syndrome
- congenital
- pseudoptosis (e.g. dermatochalasis, enophthalmos, contralateral exophthalmos)

Treatment

- surgery

Trichiasis

- eyelashes turned inwards
- may result from chronic inflammatory lid diseases (e.g. blepharitis), Stevens-Johnson syndrome, trauma, burns
- patient complains of red eye, foreign body sensation, tearing
- may result in corneal ulceration and scarring

Treatment

- topical lubrication, eyelash plucking, electrolysis, cryotherapy

Entropion

- lid margin turns in towards globe causing tearing, foreign body sensation and red eye
- most commonly affects lower lid
- may cause abrasions with secondary corneal scarring

Etiology

- involutional (aging)
- cicatricial (herpes zoster, surgery, trauma, burns)
- orbicularis oculi muscle spasm
- congenital

Treatment

- lubricants, evert lid with tape, surgery

Ectropion

- lid margin turns outward from globe causing tearing and possibly exposure keratitis



Testing for Entropion

Forced lid closure: Ask patient to tighten lid then open. In entropion, lid rolls inwards.

Testing for Ectropion

Snapback test: Pull eyelid inferiorly. In ectropion, lid remains away from globe.

Etiology

- involutional (aging)
- paralytic (CN VII palsy)
- cicatricial (burns, trauma, surgery)
- mechanical (lid edema, tumour, herniated fat)
- congenital

Treatment

- topical lubrication, surgery

**Hordeolum (Stye)**

- acute inflammation of eyelid gland – either Meibomian glands (internal lid) or glands of Zeis (modified sweat gland) or Moll (modified sebaceous gland in external lid)
- infectious agent is usually *S. aureus*
- painful, red swelling of lid

Treatment

- warm compresses, lid care, gentle massage
- topical antibiotics (e.g. erythromycin ointment BID)
- usually resolves in 2-5 days

Chalazion

- chronic granulomatous inflammation of Meibomian gland often preceded by an internal hordeolum
- acute inflammatory signs are usually absent
- differential diagnosis: basal cell carcinoma, sebaceous cell adenoma, Meibomian gland carcinoma

Treatment

- warm compresses
- if no improvement after 1 month, consider incision and curettage
- chronic, recurrent lesion must be biopsied to rule out malignancy

**Blepharitis**

- inflammation of lid margins

Etiology

- two main types
 - staphylococcal (*S. aureus*): ulcerative, dry scales
 - seborrheic: no ulcers, greasy scales

Clinical Features

- itching, tearing, foreign body sensation
- thickened, red lid margins, crusting, discharge with pressure on lids (“toothpaste sign”)

Complications

- recurrent chalazia
- conjunctivitis
- keratitis (from poor tear film)
- corneal ulceration and neovascularization

Treatment

- warm compresses and lid scrubs with diluted “baby shampoo”
- topical or systemic antibiotics as needed
- if severe, an ophthalmologist may prescribe a short course of topical corticosteroids

Xanthelasma

- eyelid xanthoma (lipid deposits in dermis of lids)
- appear as pale, slightly elevated yellowish plaques or streaks
- most commonly on the medial upper lids, often bilateral
- associated with hyperlipidemia (approximately 50% of patients)
- common in the elderly, more concerning in the young

Treatment

- excision for cosmesis only, recurrences common

Conjunctiva

- thin, vascular mucous membrane/epithelium
- **bulbar conjunctiva:** lines sclera to limbus (junction between cornea and sclera)
- **palpebral conjunctiva:** lines inner surface of eyelid

Pinguecula



- yellow-white subepithelial deposit of hyaline and elastic tissue adjacent to the nasal or temporal limbus
- associated with sun and wind exposure, aging
- common, benign, sometimes enlarge slowly
- may be irritating due to abnormal tear film formation over the deposits
- surgery for cosmesis only
- irritative symptoms may be treated with lubricating drops

Pterygium



- fibrovascular triangular encroachment of epithelial tissue onto the cornea, usually nasal
- may induce astigmatism, decrease vision
- excision for chronic inflammation, threat to visual axis, cosmesis
- irritative symptoms may be treated with lubricating drops
- one-third recur after excision, lower recurrence with conjunctival autograft (5%)

Subconjunctival Hemorrhage



- blood beneath the conjunctiva, otherwise asymptomatic
- idiopathic or associated with trauma, Valsalva maneuver, bleeding disorders, hypertension
- give reassurance if no other ocular findings, resolves in 2-3 weeks
- if recurrent, consider medical/hematologic work-up

Conjunctivitis



Etiology

- infectious
 - bacterial, viral, chlamydial, fungal, parasitic
- non-infectious
 - allergic: atopic, seasonal, giant papillary conjunctivitis (contact lens wearers)
 - toxic: irritants, dust, smoke, irradiation
 - secondary to another disorder: dacryocystitis, dacryoadenitis, cellulitis, Kawasaki's disease



- Enlarged lymph nodes suggest infectious etiology, especially viral or chlamydial conjunctivitis
- Temporal conjunctival lymphatics drain to preauricular nodes, and nasal to submandibular nodes

Clinical Features

- red eye (conjunctival injection often with limbal pallor), chemosis, subepithelial infiltrates
- itching, foreign body sensation, tearing, discharge, crusting of lashes in the morning, lid edema
- preauricular and/or submandibular nodes
- follicles: pale lymphoid elevations of the conjunctiva
- papillae: fibrovascular elevations of the conjunctiva with central network of finely branching vessels (cobblestone appearance)



- Follicles are usually seen in viral and chlamydial conjunctivitis
- Papillae are usually seen in allergic and bacterial conjunctivitis

ALLERGIC CONJUNCTIVITIS

Atopic

- associated with rhinitis, asthma, dermatitis, hay fever
- small papillae, chemosis, thickened and erythematous lids, corneal neovascularization
- seasonal (pollen, grasses, plant allergens)
- treatment: cool compresses, antihistamine, mast cell stabilizer



- Types of Discharge**
- Allergic: mucoid
 - Viral: watery
 - Bacterial: purulent
 - Chlamydial: mucopurulent

Giant Papillary Conjunctivitis (GPC)

- immune reaction to mucus debris on lenses in contact lens wearers
- large papillae form on superior palpebral conjunctiva
- treatment: clean, change or discontinue use of contact lens

Vernal Conjunctivitis

- large papillae (cobblestones) on superior palpebral conjunctiva with corneal ulcers and keratitis
- seasonal (warm weather)
- occurs in children, lasts for 5-10 years and then resolves
- treatment: consider topical steroid, cyclosporine (not in primary care)

**VIRAL CONJUNCTIVITIS**

- serous discharge, lid edema, follicles
- subepithelial corneal infiltrates
- may be associated with rhinorrhea
- preauricular node often palpable and tender
- initially unilateral, often progresses to the other eye
- mainly due to adenovirus – highly contagious for up to 12 days

Treatment

- cool compresses, topical lubrication
- usually self-limiting (7-12 days)
- proper hygiene is very important

BACTERIAL CONJUNCTIVITIS

- purulent discharge, lid swelling, papillae, conjunctival injection, chemosis
- common agents include *S. aureus*, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*
- in neonates or if sexually active must consider *N. gonorrhoeae* (invades cornea to cause keratitis)
- *Chlamydia trachomatis* is the most common cause in neonates

Treatment

- topical broad-spectrum antibiotic
- systemic antibiotics if indicated, especially in neonates and children
- usually a self-limited course of 10-14 days if no treatment, 1-3 days with treatment

CHLAMYDIAL CONJUNCTIVITIS

- caused by *Chlamydia trachomatis*
- affects neonates on day 3-5, sexually active people
- causes trachoma and inclusion conjunctivitis

Trachoma

- leading infectious cause of blindness in the world
- severe keratoconjunctivitis leads to corneal abrasion, ulceration, and scarring
- initially, follicles on superior palpebral conjunctiva
- treatment: topical and systemic tetracycline

Inclusion Conjunctivitis

- chronic conjunctivitis with follicles and subepithelial infiltrates
- most common cause of conjunctivitis in newborns
- prevention: topical erythromycin at birth
- treatment: topical and systemic tetracycline, doxycycline or erythromycin

Sclera

- the white fibrous outer protective coat of the eye
- continuous with the cornea anteriorly and the dura of the optic nerve posteriorly
- episclera is a thin layer of vascularized tissue between the sclera and conjunctiva

Episcleritis

- immunologically mediated inflammation of episclera
- one-third bilateral; simple (80%) or nodular (20%)
- more frequent in women than men (3:1)

Etiology

- mostly idiopathic
- in 1/3 of cases, associated with collagen vascular diseases, infections (herpes zoster, herpes simplex, syphilis), inflammatory bowel disease, rosacea, atopy

Clinical Features

- asymptomatic usually, may have mild pain and red eye
- sectoral or diffuse injection of radially-directed vessels, chemosis, small mobile nodules
- blanches with topical phenylephrine (constricts superficial conjunctival vessels)

Treatment

- generally self limited, recurrent in 2/3 of cases
- topical steroid for 3-5 days if painful (prescribed and monitored by ophthalmologist)



To differentiate between episcleritis and scleritis, place a drop of phenylephrine 2.5% (Mydrin®; AK-Dilate®) in the affected eye. Re-examine the vascular pattern 10-15 minutes later. Episcleral vessels should blanch. Scleral vessels do not.

Scleritis

- usually bilateral: diffuse, nodular or necrotizing
- anterior scleritis: may cause scleral thinning
- posterior scleritis: may cause exudative retinal detachment
- more common in women and elderly

Etiology

- may be a manifestation of systemic disease
- collagen vascular disease, e.g. systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS)
- granulomatous, e.g. tuberculosis (TB), sarcoidosis, syphilis
- metabolic, e.g. gout, thyrotoxicosis
- infectious, e.g. *S. aureus*, *S. pneumoniae*, *P. aeruginosa*, herpes zoster
- chemical or physical agents, e.g. thermal, alkali or acid burns
- idiopathic

Clinical Features

- severe pain, photophobia, red eye, decreased vision
- pain is best indicator of disease progression
- inflammation of scleral, episcleral and conjunctival vessels
- may have anterior chamber cells/flare, corneal infiltrate, scleral thinning
- sclera may have a blue hue best seen in natural light, due to scleral thinning and visualization of underlying choroid pigment
- scleral edema or thinning
- failure to blanch with topical phenylephrine

Treatment

- systemic NSAID or steroid (topical steroids are not effective)
- treat underlying etiology

**Scleromalacia Perforans**

- Anterior necrotizing scleritis without inflammation and asymptomatic
- Strongly associated with rheumatoid arthritis
- May result in scleral thinning
- Traumatic perforation can easily occur – examine eye very gently

Cornea

- function
 - transmission of light
 - refraction of light (2/3 of total refractive power of eye)
 - barrier against infection, foreign bodies
- transparency due to avascularity, uniform structure and deturgescence (relative dehydration)
- 5 layers (anterior to posterior): epithelium, Bowman's membrane, stroma, Descemet's membrane, endothelium (dehydrates the cornea; dysfunction = corneal edema)
- extensive sensory fibre network (V1 distribution); therefore abrasions and inflammation (keratitis) are very painful

Foreign Body

- foreign material in or on cornea
- may have associated rust ring if metallic
- patients may note tearing, photophobia, foreign body sensation, red eye
- signs include foreign body, conjunctival injection, epithelial defect that stains with fluorescein, corneal edema, anterior chamber cells/flare

Complications

- abrasion, infection, scarring, rust ring, secondary iritis

Treatment

- remove under magnification using local anesthetic and sterile needle or refer to ophthalmology (depending on depth and location)
- treat as per corneal abrasion



Foreign body behind lid may cause multiple vertical corneal epithelial abrasions due to blinking.



Topical analgesics should only be used to facilitate examination. They should NEVER be used as treatment for any ocular problem.



NEVER patch abrasion if patient wears contact lenses (prone to *Pseudomonas* infection).



Corneal abrasions from organic matter (e.g. twig, finger nail, etc.) have higher recurrence, even years later.



Corneal Abrasion: To Patch or Not to Patch

Patching for corneal abrasion. *Cochrane Review 2006*

Patching is not indicated for simple corneal abrasions, measuring less than 10 mm. There is no improvement in healing rates on days 1-3, no changes in reported pain and no difference in the use of antibiotics between the patch and non-patch groups.

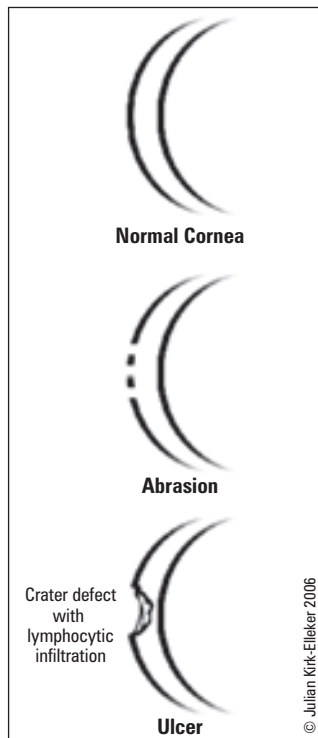


Figure 14. Corneal Abrasion vs. Ulcer

Corneal Abrasion

- epithelial defect usually due to trauma (e.g. fingernails, paper, twigs), contact lens (Figure 14)

Clinical Features (Table 5)

- pain, redness, tearing, photophobia, foreign body sensation
- de-epithelialized area stains with fluorescein dye
- pain relieved with topical anesthetic

Complications

- infection, ulceration, recurrent erosion, secondary iritis

Treatment

- topical antibiotic (drops or ointment)
- consider topical NSAID, cycloplegic (relieves pain and photophobia by paralyzing ciliary muscle), patch
- most abrasions clear spontaneously within 24-48 hours

Recurrent Erosions

- recurrent episodes of pain, photophobia, foreign body sensation with a spontaneous corneal epithelial defect
- usually occurs upon awakening
- associated with improper adherence of epithelial cells to the underlying basement membrane

Etiology

- previous traumatic corneal abrasion
- corneal dystrophy
- idiopathic

Treatment

- as for corneal abrasion until re-epithelialization occurs
- topical hypertonic saline ointment, topical lubrication
- bandage contact lens, anterior stromal puncture or phototherapeutic keratectomy for chronic recurrences

Corneal Ulcer

Etiology

- local necrosis of corneal tissue due to infection (Figure 14)
- infection is usually bacterial, rarely viral, fungal or protozoan (*Acanthamoeba*)
- secondary to corneal exposure, abrasion, foreign body, **contact lens use** (50% of ulcers)
- also associated with conjunctivitis, blepharitis, keratitis, vitamin A deficiency

Clinical Features

- pain, photophobia, tearing, foreign body sensation, decreased visual acuity (if central ulcer)
- corneal opacity that necroses and forms an excavated ulcer with infiltrative base
- overlying corneal epithelial defect that stains with fluorescein
- may develop corneal edema, conjunctival injection, anterior chamber cells/flare, hypopyon, corneal hypoesthesia (in viral keratitis)
- bacterial ulcers may have purulent discharge, viral ulcers may have watery discharge

Complications

- decreased vision, corneal perforation, iritis, endophthalmitis

Treatment

- urgent referral to ophthalmology
- culture first
- topical antibiotics every hour
- must treat vigorously to avoid complications

Table 5. Corneal Abrasion vs. Corneal Ulcer

	Abrasion	Ulcer
Time Course	Acute (instantaneous)	Subacute (days)
History of Trauma	Yes	Not usually
Cornea	Clear	White, necrotic area
Iris Detail	Clear	Obscured
Corneal Thickness	Normal	May have crater defect/thinning
Extent of Lesion	Limited to epithelium	Extension into stroma



Abrasion vs. Ulcer on Slit Lamp
An abrasion appears clear while an ulcer is more opaque.

Herpes Simplex Keratitis



- usually HSV type 1 (90% of population are carriers)
- may be triggered by stress, fever, sun exposure, immunosuppression

Clinical Features

- pain, tearing, foreign body sensation, red eye, may have decreased vision, eyelid edema
- corneal hypoesthesia
- dendritic (thin and branching) lesion in epithelium that stains with fluorescein

Complications

- corneal scarring (can lead to loss of vision)
- chronic interstitial keratitis due to penetration of virus into stroma
- secondary iritis, secondary glaucoma

Treatment

- topical antiviral such as trifluridine, consider systemic antiviral such as acyclovir
- dendritic debridement
- NO STEROIDS initially – may exacerbate condition
- ophthalmologist must exercise caution if adding topical steroids for chronic keratitis or iritis

Herpes Zoster

- dermatitis of the forehead (the CN V1 territory) may involve the globe (Figure 15)
- Hutchinson's sign: if tip of nose is involved (nasociliary branch of V1) then eye will be involved in approximately 75% of cases
- if no nasal involvement, the eye is involved in 1/3 of patients

Clinical Features

- pain, tearing, photophobia, red eye
- corneal edema, pseudodendrite, superficial punctate keratitis
- corneal hypoesthesia

Complications

- corneal keratitis, ulceration, perforation and scarring
- secondary iritis, secondary glaucoma, cataract
- muscle palsies (rare) due to CNS involvement
- occasionally severe post-herpetic neuralgia

Treatment

- oral antiviral (acyclovir, valacyclovir or famciclovir) immediately
- topical steroids, cycloplegia as indicated for keratitis, iritis
- erythromycin ointment if conjunctival involvement

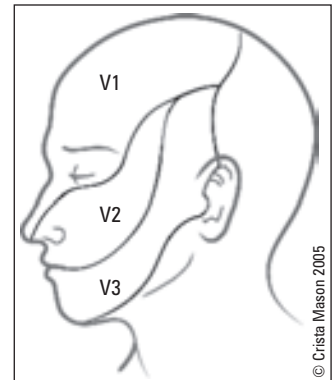


Figure 15. Trigeminal Distribution



Steroid treatment for ocular disorders should only be prescribed and supervised by an ophthalmologist, as they can impair corneal healing and exacerbate herpetic keratitis.

Keratoconus

- bilateral paracentral thinning and bulging (ectasia) of the cornea to form a conical shape
- usually sporadic, but associated with Down's syndrome, atopy, contact lens use (theorized to be related to chronic vigorous eye rubbing)
- associated with breaks in Descemet's and Bowman's membrane
- results in irregular astigmatism, scarring, stromal edema

Treatment

- attempt correction with spectacles or contact lens
- cross-linking laser treatment may halt or slow disease progression
- penetrating keratoplasty (corneal transplant) 90% successful
- post-operative complications: endophthalmitis, graft rejection, graft failure, graft dehiscence



To detect keratoconus, look for bulging of the lower eyelid when the patient looks downward (Munson's sign).

Arcus Senilis

- hazy white ring in peripheral cornea, <2 mm wide, clearly separated from limbus
- common, bilateral, benign corneal degeneration due to lipid deposition, part of the aging process
- may be associated with hypercholesterolemia if age <40 years, check lipid profile
- no associated visual symptoms, no complications, no treatment necessary

Kayser-Fleischer Ring

- brown-yellow-green pigmented ring in peripheral cornea, starting inferiorly
- due to deposition of copper pigment in Descemet's membrane
- associated with Wilson's disease (95%, hepatolenticular degeneration)
- no associated symptoms or complications of ring
- treat underlying disease

The Uveal Tract

- uveal tract = iris, ciliary body, choroid
- vascularized, pigmented middle layer of the eye, between the sclera and the retina

Uveitis

- may involve one or all three parts of the tract
- idiopathic or associated with autoimmune, infectious, granulomatous, malignant causes
- should be managed by an ophthalmologist

Anterior Uveitis (Iritis)

- inflammation of iris, usually accompanied by cyclitis (inflammation of ciliary body), when both = iridocyclitis
- usually unilateral

Etiology

- usually idiopathic
- connective tissue diseases
 - HLA-B27: reactive arthritis, ankylosing spondylitis (AS), psoriatic arthritis, inflammatory bowel disease (IBD)
 - non-HLA-B27: juvenile idiopathic arthritis (JIA)
- infectious: syphilis, Lyme disease, toxoplasmosis, TB, HSV, herpes zoster
- other: sarcoidosis, trauma, large abrasion, post ocular surgery

Clinical Features

- photophobia (due to reactive spasm of inflamed iris muscle), ocular pain, tenderness of the globe, brow ache (ciliary muscle spasm), decreased visual acuity, tearing
- ciliary flush (perilimbal conjunctival injection), miosis (spasm of sphincter muscle) (Figure 16)
- anterior chamber "cells" (WBC in anterior chamber due to anterior segment inflammation) and "flare" (protein precipitates in anterior chamber secondary to inflammation), hypopyon (collection of neutrophilic exudates inferiorly in the anterior chamber)
- occasionally keratic precipitates (clumps of cells on corneal endothelium)
- iritis typically reduces intraocular pressure because ciliary body inflammation causes decreased aqueous production; however, severe iritis, or iritis from herpes simplex and zoster may cause an inflammatory glaucoma

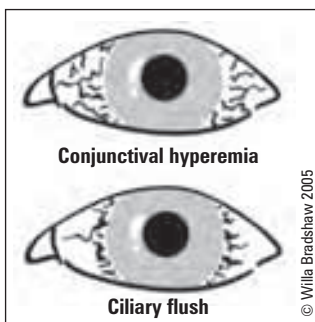


Figure 16. Conjunctival Hyperemia vs. Ciliary Flush

Complications

- inflammatory glaucoma
- posterior synechiae
 - adhesions of posterior iris to anterior lens capsule
 - indicated by an irregularly shaped pupil
 - if occurs 360°, entraps aqueous in posterior chamber, iris bows forward "iris bombe" → angle closure glaucoma
- peripheral anterior synechiae (PAS) (rare): adhesions of iris to cornea → glaucoma
- cataracts
- band keratopathy (with chronic iritis)
 - superficial corneal calcification keratopathy
- macular edema with chronic iritis

Treatment (by ophthalmologists)

- mydriatics: dilate pupil to prevent formation of posterior synechiae and to decrease pain from ciliary spasm
- steroids: topical, subconjunctival or systemic
- systemic analgesia
- medical workup may be indicated

Posterior Uveitis (Choroiditis)



- inflammation of the choroid

Etiology

- bacterial: syphilis, tuberculosis
- viral: herpes simplex virus, cytomegalovirus in AIDS
- fungal: histoplasmosis, candidiasis
- parasitic: toxoplasmosis (most common cause), toxocara
- immunosuppression may predispose to any of the above infections
- autoimmune: Behçet's disease (triad of oral ulcers, genital ulcers, and posterior uveitis)
- malignancies (masquerade syndrome): metastatic lesions, malignant melanoma

Clinical Features

- painless as choroid has no sensory innervation
- often no conjunctival or scleral injection present
- decreased visual acuity
- floaters (debris and inflammatory cells)
- vitreous cells and opacities
- hypopyon formation

Treatment

- steroids: retrobulbar or systemic if indicated (e.g. threat of vision loss)

Lens

- consists of an outer capsule surrounding a soft cortex and a firm inner nucleus

Cataracts



- any opacity of the lens
- most common cause of reversible blindness worldwide
- types: nuclear sclerosis, cortical, posterior subcapsular (Figure 17)

Etiology

- acquired
 - age-related (over 90% of all cataracts)
 - cataract associated with systemic disease (may have juvenile onset)
 - ♦ diabetes mellitus
 - ♦ metabolic disorders (e.g. Wilson's disease, galactosemia, homocystinuria)
 - ♦ hypocalcemia
 - traumatic (may be rosette shaped)
 - intraocular inflammation (e.g. uveitis)
 - toxic (steroids, phenothiazines)
 - radiation
- congenital
 - present with altered red reflex or leukocoria
 - treat promptly to prevent amblyopia

Clinical Features

- gradual, painless, progressive decrease in visual acuity
- glare, dimness, halos around lights at night, monocular diplopia
- "second sight" phenomenon – patient is more myopic than previously noted, due to increased refractive power of the lens (in nuclear sclerosis only)
 - patient may read without previously needed reading glasses
- diagnose by slit-lamp exam, and by noting changes in red reflex using ophthalmoscope
- may impair view of retina during funduscopy

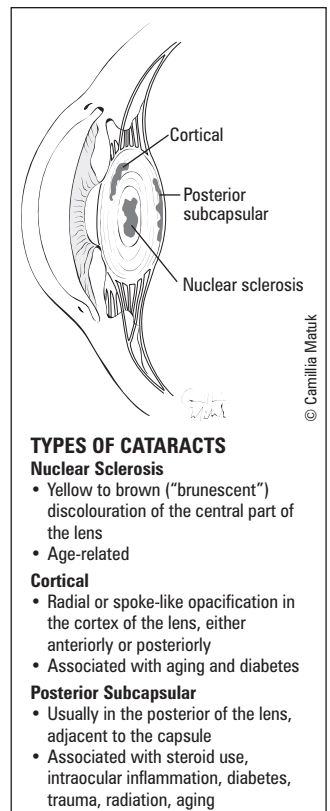


Figure 17. Types of Cataracts

Treatment

- medical: attempt correction of refractive error
- surgical: definitive treatment
 - indications for surgery
 - ♦ to improve visual function in patients whose visual loss leads to functional impairment (patients may be inclined to postpone surgery as long as one eye has sufficient vision)
 - ♦ to aid management of other ocular disease (e.g. cataract that prevents adequate retinal exam or laser treatment of diabetic retinopathy)
 - ♦ congenital or traumatic cataracts
 - phacoemulsification (phaco = lens)
 - ♦ most commonly used surgical technique (see *Surgical Ophthalmology*, OP43)
 - post-operative complications
 - ♦ retinal detachment, endophthalmitis, dislocated IOL, macular edema, glaucoma
 - ♦ with new foldable IOLs that have truncated edges, <10% of patients get posterior capsular opacification (PCO), which is treated with YAG laser

Prognosis

- excellent if not complicated by other ocular disease



Dislocated Lens (Ectopia Lentis)

Etiology

- associated with Marfan's Syndrome, Ehlers-Danlos type VI, homocystinuria, syphilis, lens coloboma (congenital cleft due to failure of ocular adnexa to complete growth)
- traumatic

Clinical Features

- decreased visual acuity
- may get unilateral diplopia
- iridodonesis (quivering of iris with movement)
- direct ophthalmoscopy may elicit abnormal red reflex

Complications

- cataract, glaucoma, uveitis

Treatment

- surgical correction ± lens replacement

Vitreous



Floater = "bugs", "cobwebs" or "spots" that change with eye position.

- clear gel (99% water plus collagen fibrils, glycosaminoglycans and hyaluronic acid) that fills the posterior segment of eye
- normally adherent to optic disc, pars plana, and along major retinal blood vessels
- central vitreous commonly shrinks and liquefies with age (syneresis)
- during syneresis, the molecules that held water often condense, causing vitreous floaters
- floaters are usually harmless, but retinal tear/detachment and hemorrhagic diseases must be ruled out

Posterior Vitreous Detachment (PVD)

Etiology

- normal aging process of vitreous liquification (syneresis)
- liquid vitreous moves between posterior vitreous gel and retina
- vitreous is peeled away and separates from the retina

Clinical Features

- floaters, flashes of light

Complications

- traction at areas of abnormal vitreoretinal adhesions may cause retinal tears/detachment
- retinal tears/detachment may cause vitreous hemorrhage if tear bridges blood vessel
- complications more common in high myopes and following ocular trauma (blunt or perforating)

Treatment

- acute onset of PVD requires a dilated fundus exam to rule out retinal tears/detachment
- no specific treatment available for floaters/flashes of light



Weiss' Ring – glial tissue around the optic disc remains attached to posterior vitreous.



New or a marked increase in floaters and/or flashes of light requires a dilated fundus exam to rule out retinal tears/detachment.

Vitreous Hemorrhage

- bleeding into the vitreous cavity

Etiology

- proliferative diabetic retinopathy (PDR)
- retinal tear/detachment
- posterior vitreous detachment (PVD)
- retinal vein occlusion
- trauma

Clinical Features

- sudden loss of visual acuity
- may be preceded by many floaters and/or flashes of light
- ophthalmoscopy: no red reflex if large hemorrhage, retina not visible due to blood in vitreous

Treatment

- ultrasound (B-scan) to rule out retinal detachment
- expectant: in non-urgent cases (e.g. no retinal detachment), blood usually resorbs in 3-6 months
- surgical: vitrectomy ± retinal detachment repair ± retinal endolaser to possible bleeding sites/vessels



Any time a vitreous or retinal hemorrhage is seen in a child, must rule out child abuse.



Common causes of vitreous hemorrhage are proliferative diabetic retinopathy and retinal tears.

Endophthalmitis and Vitritis

- intraocular infection: acute, subacute or chronic

Etiology

- most commonly a postoperative complication; risk following cataract surgery is <0.1%
- also due to penetrating injury to eye (risk is 3-7%), endogenous spread, and intravitreal injections
- etiology usually bacterial, may be fungal

Clinical Features

- very painful, red eye, photophobia, discharge
- severely reduced visual acuity, lid edema, proptosis, corneal edema, anterior chamber cells/flare, hypopyon, reduced red reflex
- may have signs of a ruptured globe (severe subconjunctival hemorrhage, hyphema, decreased intraocular pressure, etc.)

Treatment

- **OCULAR EMERGENCY:** presenting vision best indicates prognosis
- LP or worse – admission, immediate vitrectomy and intravitreal antibiotics to prevent loss of vision
- HM or better – vitreous tap for culture and intravitreal antibiotics
- topical fortified antibiotics



Remember to inquire about tetanus status in post-traumatic endophthalmitis.

Endophthalmitis Vitrectomy Study

Endophthalmitis Vitrectomy Study Group. Results of the Endophthalmitis Vitrectomy Study. *Archives of Ophthalmology* 1995; 113 (12):1479-96

For treatment of post-cataract surgery

endophthalmitis:

- Intravitreal antibiotics preferred over systemic antibiotics
- Vitrectomy indicated only if vision LP or worse

Retina

- composed of two parts (Figure 2)
 - neurosensory retina – comprises 9 of the 10 retinal layers, including the photoreceptors and the ganglion cell layer
 - retinal pigment epithelium (RPE) layer – external to neurosensory retina
- macula: rich in cones (for colour vision); most sensitive area of retina; looks darker due to lack of retinal vessels and thinning of retina in this region; 15° temporal and slightly below the optic disc
- fovea: centre of macula; responsible for acute, fine vision
- optic disc: slightly oval vertically, pinkish colour with centrally depressed yellow cup (normal cup:disc ratio is <0.5), retinal artery and vein pass through cup
- ora serrata: irregularly-shaped, anterior margin of the retina (can only be visualized with indirect ophthalmoscopy of the far peripheral retina, or through a Goldmann 3 mirror lens)





Central Retinal Artery Occlusion (CRAO)

Etiology

- emboli from carotid arteries or heart (e.g. arrhythmia, endocarditis, valvular disease)
- thrombus
- temporal arteritis

Clinical Features

- sudden, painless (except in temporal arteritis), severe monocular loss of vision
- relative afferent pupillary defect (RAPD)
- patient will often have experienced transient episodes in the past (amaurosis fugax)
- fundoscopy
 - “cherry-red spot” at centre of macula (visualization of unaffected highly vascular choroid through the thin fovea)
 - retinal pallor
 - narrowed arterioles, boxcarring (segmentation of blood in arteries)
 - cotton-wool spots (retinal infarcts)
 - cholesterol emboli (Hollenhorst plaques) – usually located at arteriole bifurcations
 - after ~6 weeks: cherry-red spot recedes and optic disc pallor becomes evident

Treatment

- **OCULAR EMERGENCY:** attempt to restore blood flow within 2 hours
- the sooner the treatment = better prognosis (irreversible retinal damage if >90 min of complete CRAO)
 - massage the globe (compress eye with heel of hand for 10 s, release for 10 s, repeat for 5 min) to dislodge embolus
 - decrease intraocular pressure
 - ♦ topical beta-blockers
 - ♦ inhaled oxygen-carbon dioxide mixture
 - ♦ IV Diamox® (carbonic anhydrase inhibitor)
 - ♦ IV mannitol (draws fluid from eye)
 - ♦ drain aqueous fluid – anterior chamber paracentesis (carries risk of endophthalmitis)
 - treat underlying cause to prevent CRAO in fellow eye
 - follow up 1 month to rule out neovascularization



Treatment for a central retinal artery occlusion (CRAO) must be initiated within 2 hours of symptom onset for any hope of restoring vision.

Branch Retinal Artery Occlusion (BRAO)

- only part of the retina becomes ischemic resulting in a visual field loss
- more likely to be of embolic etiology than CRAO; need to search for source
- management: ocular massage to dislodge embolus if visual acuity is affected



Central/Branch Retinal Vein Occlusion (CRVO/BRVO)

- second most frequent “vascular” retinal disorder after diabetic retinopathy
- usually a manifestation of a systemic disease (e.g. hypertension, diabetes mellitus)
- thrombus occurs within the lumen of the blood vessel

Predisposing Factors

- arteriosclerotic vascular disease
- hypertension
- diabetes mellitus
- glaucoma
- hyperviscosity (e.g. polycythemia rubra vera, sickle-cell disease, lymphoma, leukemia)
- drugs [e.g. oral contraceptive pill (OCP), diuretics]

Clinical Features

- painless, monocular, gradual or sudden visual loss
- ± RAPD
- fundoscopy
 - “blood and thunder” appearance
 - diffuse retinal hemorrhages, cotton-wool spots, venous engorgement, swollen optic disc, macular edema
- two fairly distinct groups
 - **venous stasis/non-ischemic retinopathy**
 - ♦ no RAPD, VA approximately 20/80
 - ♦ mild hemorrhage, few cotton wool spots
 - ♦ resolves spontaneously over weeks to months
 - ♦ may regain normal vision if macula intact



The “blood and thunder” appearance on fundoscopy is very characteristic of a central retinal vein occlusion (CRVO).

Branch Vein Occlusion Study (BVOS)
Branch Vein Occlusion Study Group: Argon laser photocoagulation for macular edema in branch vein occlusion. *Am J Ophthalmol* 1984 98: 271-282, BVOS showed that argon laser treatment improves sight significantly in patients with macular edema following BRVO. The treatment also decreases the risk of vitreous hemorrhage.

- **hemorrhagic/ischemic retinopathy**
 - ♦ usually older patient with deficient arterial supply
 - ♦ RAPD, VA approximately 20/200, reduced peripheral vision
 - ♦ more hemorrhages, cotton wool spots, congestion
 - ♦ poor visual prognosis



8-10% risk of developing CRVO or BRVO in other eye.

Complications

- degeneration of retinal pigment epithelium
- neovascularization of retina and iris (secondary rubeosis), leading to secondary glaucoma
- vitreous hemorrhage
- macular edema

Treatment

- no treatment available to restore vision in CRVO/BRVO
- treat underlying cause/contributing factor
- fluorescein angiography to determine extent of retinal non-perfusion = risk of neovascularization
- retinal laser photocoagulation, intravitreal corticosteroid or anti-VEGF injection to reduce neovascularization and prevent neovascular glaucoma

Retinal Detachment (RD)



- cleavage in the plane between the neurosensory retina and the retinal pigment epithelium (RPE)
- three types
 - **rhematogenous** (most common)
 - ♦ caused by a tear or hole in the neurosensory retina, allowing fluid from the vitreous to pass into the subretinal space
 - ♦ tears may be caused by posterior vitreous detachment (PVD), degenerative retinal changes, trauma or iatrogenically
 - ♦ incidence increases with advancing age, in high myopes and after ocular surgery/trauma
 - **tractional**
 - ♦ caused by traction (due to vitreal, epiretinal or subretinal membrane) pulling the neurosensory retina away from the underlying RPE
 - ♦ found in conditions such as diabetic retinopathy, CRVO, sickle cell disease, retinopathy of prematurity (ROP), and ocular trauma
 - **exudative**
 - ♦ caused by damage to the RPE resulting in fluid accumulation in the subretinal space
 - ♦ main causes are intraocular tumours, posterior uveitis, central serous retinopathy



Superotemporal retina is the most common site for horseshoe tears.

Clinical Features

- sudden onset
- flashes of light
 - due to mechanical stimulation of the retinal photoreceptors
- floaters
 - hazy spots in the line of vision which move with eye position, due to drops of blood from torn vessels bleeding into the vitreous
- curtain of blackness/peripheral field loss
 - darkness in one field of vision when the retina detaches in that area
- loss of central vision (if macula "off")
- decreased IOP (usually 4-5 mmHg lower than the other, normal eye)
- ophthalmoscopy: detached retina is grey-white with surface blood vessels, loss of red reflex
- ± RAPD

Treatment

- prophylactic: symptomatic tear (flashes or floaters) can be sealed off with laser/cryotherapy, with the goal of preventing progression to detachment
- therapeutic
 - **rhematogenous**
 - ♦ scleral buckle procedure (see *Surgical Ophthalmology*, OP43)
 - ♦ pneumatic retinopexy (see *Surgical Ophthalmology*, OP43)
 - ♦ both above treatments are used in combination with localization of retinal tears/holes and subsequent treatment with diathermy, cryotherapy or laser to create adhesions between the RPE and the neurosensory retina
 - ♦ vitrectomy plus injection of silicone oil in cases of recurrent detachment
 - **tractional**
 - ♦ vitrectomy ± membrane removal/scleral buckling/injection of intraocular gas as necessary
 - **exudative**
 - ♦ treat underlying cause

Complications

- loss of vision, vitreous hemorrhage, recurrent retinal detachment
- a retinal detachment is an emergency, especially if the macula is still attached (macula “on”)
- prognosis for visual recovery varies inversely with the amount of time the retina is detached and whether the macula is attached or not

Retinitis Pigmentosa



Triad of Retinitis Pigmentosa

APO

Arteriolar narrowing
Perivascular bony-spicule pigmentation
Optic disc pallor

- worldwide incidence between 1/3500 and 1/7000 people
- many forms of inheritance, most commonly autosomal recessive (60%)
- hereditary degenerative disease of the retina manifested by rod > cone photoreceptor degeneration and retinal atrophy
- symptoms: night blindness, decreased peripheral vision (“tunnel vision”), decreased central vision (macular changes), glare (from cataract)
- funduscopy: areas of “bone-spicule” pigment clumping in mid-periphery of retina, narrowed retinal arterioles, pale optic disc
- electrophysiological tests (ERG, EOG) assist in diagnosis
- management: no treatments available to reverse the condition; cataract extraction improves visual function

Age-Related Macular Degeneration (ARMD)

Age-related Eye Disease Study (AREDS)

*The Age-Related Eye Disease Research Group:
A randomized, placebo-controlled, clinical trial of
high-dose supplementation with vitamins C and E,
beta-carotene, and zinc for age-related macular
degeneration and vision loss. AREDS Report No. 8.
Arch Ophthalmol 2001; 119:1417-1436*
AREDS studied the effect of high-dose combination
of vitamin C, vitamin E, beta-carotene, and zinc in
patients with and without ARMD. Those who are
already affected by ARMD showed 19% decrease
in risk of further visual loss, whereas this treatment
showed no benefit in patients with early or no
ARMD.

- leading cause of irreversible blindness in the western world, associated with increasing age, usually bilateral
- 10% of people >65 years old have some degree of ARMD
- female > male
- degenerative changes are concentrated at the macula thus only central vision is lost; peripheral vision (important for navigation) is maintained so patients can usually maintain an independent lifestyle

Classification

- **Non-Exudative/“Dry” (Non-Neovascular) ARMD**
 - most common type of ARMD (90% of cases)
 - slowly progressive loss of visual function
 - drusen: pale, yellow-white deposits between the retinal pigment epithelium (RPE) and Bruch’s membrane (area separating inner choroidal vessels from RPE)
 - RPE atrophy: coalescence of depigmented RPE, clumps of focal hyperpigmentation or hypopigmentation
 - may progress to neovascular ARMD
- **Exudative/“Wet” (Neovascular) ARMD**
 - 10% of ARMD, but 80% of ARMD resulting in severe visual loss
 - choroidal neovascularization: drusen predispose to breaks in Bruch’s membrane causing subsequent growth and proliferation of choroidal capillaries
 - may get serous detachment of overlying RPE and retina, hemorrhage and lipid precipitates into subretinal space
 - can also get an elevated subretinal mass due to fibrous metaplasia of hemorrhagic retinal detachment
 - leads to disciform scarring and severe central visual loss

Risk Factors

- female
- increased age
- family history
- smoking
- Caucasian race
- blue irides

Clinical Features

- variable degree of progressive central visual loss
- metamorphopsia (distorted vision characterized by straight parallel lines appearing convergent or wavy) due to macular edema



Wet ARMD Lesions on Fluorescein Angiography

Classic: well-defined leakage
Occult: mottled or ill-defined leakage



Drusen vs. Exudate

Drusen: hyaline material secreted by RPE seen frequently in ARMD typically in peri-macular region
Hard/Soft Exudates: lipid deposits in the retina associated with diabetic retinopathy and hypertension

Investigations

- Amsler grid: held at normal reading distance with glasses on, assesses macular function
- fluorescein angiography (FA): assess degree of neovascularization – pathologic new vessels leak dye

Treatment

- non-neovascular “dry” ARMD
 - monitor, Amsler grid allows patients to check for metamorphopsia
 - low vision aids (e.g. magnifiers, closed-circuit television)
 - anti-oxidants, green leafy vegetables
 - sunglasses/visors
 - see AREDS sidebar
- neovascular “wet” ARMD
 - see *Common Medications*
 - laser photocoagulation for neovascularization
 - 50% of choroidal neovascularization cannot be treated initially
 - no definitive treatment for disciform scarring
 - photodynamic therapy (PDT) with verteporfin (Visudyne®)
 - ♦ IV injection of verteporfin followed by low intensity laser to area of choroidal neovascularization
 - ♦ Photodynamic Therapy Study Group showed that for patients with subfoveal lesions in ARMD with predominantly classic choroidal neovascularization, verteporfin treatment can reduce the risk of moderate vision loss for at least 2 years; this therapy cannot stop or reverse vision loss
 - intravitreal injection of anti-angiogenesis growth factor (anti-VEGF)
 - ♦ pegaptanib (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®)

Anti-angiogenic Therapy with Anti-vascular Endothelial Growth Factor Modalities for Neovascular Age-related Macular Degeneration
Cochrane Database of Systematic Reviews 2008, Issue 2

Study: Cochrane systematic review of RCTs investigating the use of anti-VEGF (vascular endothelial growth factor) modalities for the treatment of wet age-related macular degeneration (ARMD).

Patients: Classic or occult wet type ARMD.
Interventions: Pegaptanib/Macugen® (aptamer comprised of ribonucleic acids that bind VEGF), ranibizumab/Lucentis® (anti VEGF fragment antibody) and verteporfin/Visudyne® photodynamic therapy (PDT).

Results: The MARINA trial showed that the pooled relative risk (RR) for a gain of 15 or more letters of visual acuity was 5.81 for ranibizumab versus placebo, while the FOCUS trial showed that the pooled RR for a gain of 15 or more letters at one year was 4.44 for a combination of ranibizumab + verteporfin PDT versus verteporfin PDT alone.

Conclusions: Ranibizumab are of significant benefit for the treatment of wet ARMD with significant improvements in best corrected visual acuity at one year.

Glaucoma

Definition

- progressive optic neuropathy involving characteristic structural changes to optic nerve head with associated visual field changes
- commonly associated with high IOP, but not required for diagnosis

Background

- aqueous is produced by the ciliary body and flows from the posterior chamber to the anterior chamber through the pupil, and drains into the episcleral veins via the trabecular meshwork and Canal of Schlemm (Figure 18)
- an isolated increase in IOP is termed ocular hypertension (or glaucoma suspect) and these patients should be followed for increased risk of developing glaucoma (10% if IOP = 20-30 mmHg; 40% if IOP = 30-40 mmHg; and most if IOP >40 mmHg)
- pressures >21 mmHg are more likely to be associated with glaucoma; however, up to 50% of patients with glaucoma do not have IOP >21 mmHg
- be suspicious of glaucoma if C:D ratio >0.6, C:D ratio difference between eyes >0.2, or cup approaches disc margin
- loss of peripheral vision most commonly precedes central loss
- sequence of events: gradual pressure rise → increased C:D ratio → visual field loss
- screening tests should include
 - medical and family history
 - visual acuity testing
 - slit lamp exam to assess anterior chamber depth
 - ophthalmoscopy to assess the disc features
 - tonometry by applanation or indentation to measure the IOP
 - visual field testing

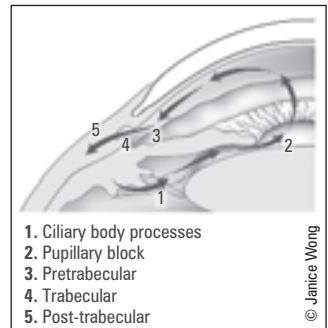


Figure 18. Aqueous Flow and Sites of Potential Resistance



Average IOP = 15 ± 3 mmHg
Normal cup:disc ≤ 0.4

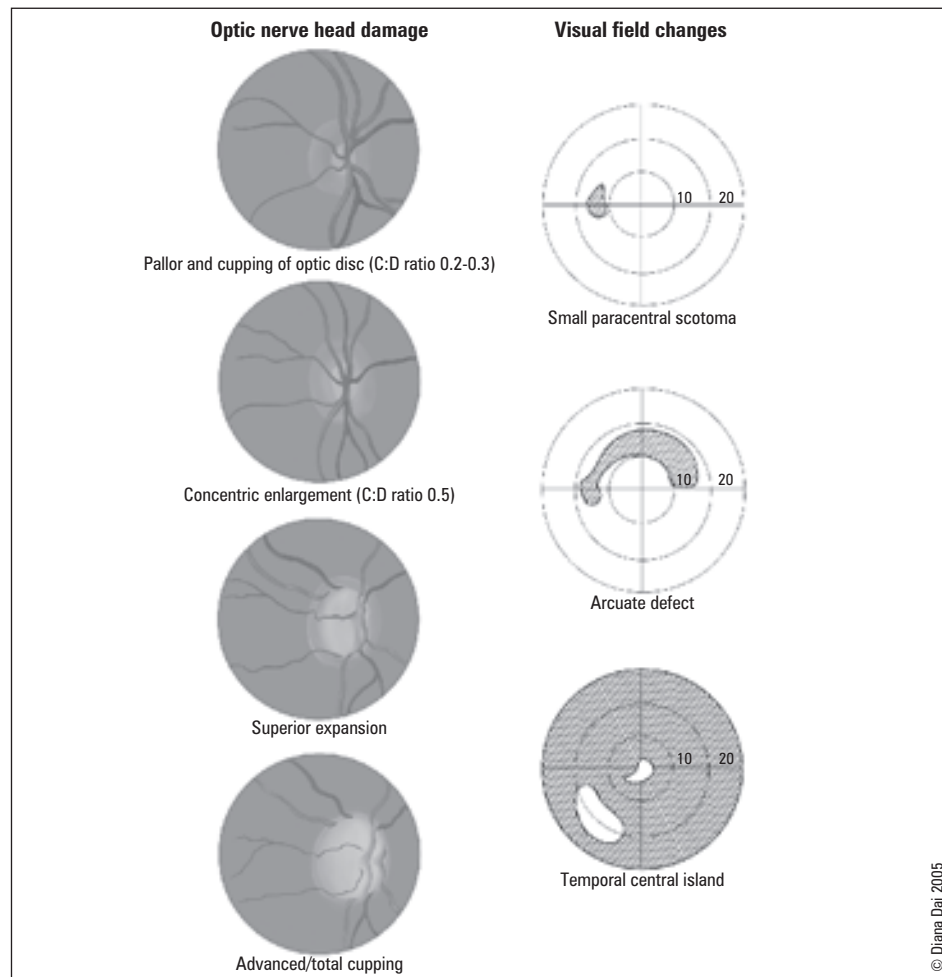


Figure 19. Glaucomatous Damage

Open- and Closed-Angle Glaucoma**POAG**

- Common (95%)
- Chronic course
- Painless eye without redness
- Moderately ↑ IOP
- Normal cornea and pupil
- No N/V
- No halos around light

PACG

- Rare (5%)
- Acute onset
- Painful red eye
- Extremely ↑ IOP
- Hazy cornea
- Mid-dilated pupil unreactive to light
- ± N/V, abdominal pain
- Halos around light

**Risk Factors for POAG****A FIAT**

- Age
- Family History
- IOP
- African descent
- Thin Cornea

**Contraindications to Dilating**

- Neurological abnormality requiring pupil assessment
- Shallow anterior chamber
- Iris-supported anterior chamber IOL

Primary Open Angle Glaucoma (POAG)

- most common form, >95% of all glaucoma cases
- due to obstruction of aqueous drainage within the trabecular meshwork and its drainage into the Canal of Schlemm
- insidious and asymptomatic, so screening is critical for early detection

Major Risk Factors

- elevated intraocular pressure (>21 mmHg)
- age: prevalence in 40 y.o. is 1-2% and in 80 y.o. 10%
- ethnicity: African descent
- familial (2-3x increased risk); polygenic

Minor Risk Factors

- myopia
- hypertension
- diabetes
- hyperthyroidism (Graves' disease)
- chronic topical ophthalmic steroid use in steroid responders – yearly eye exams recommended if >4 weeks of steroid use
- previous ocular trauma
- anemia/hemodynamic crisis (ask about blood transfusions in past)

Clinical Features

- asymptomatic initially
- insidious, painless, gradual rise in IOP due to restriction of aqueous outflow
- bilateral, but usually asymmetric
- earliest signs are optic disc changes
 - increased cup:disc ratio (vertical C:D >0.6)
 - significant cup:disc asymmetry between eyes (>0.2 difference)

- thinning, notching of the neuroretinal rim
- flame shaped disc hemorrhage
- 360° of peripapillary atrophy
- nerve fibre layer defect
- large vessels become nasally displaced
- visual field loss
 - slow, progressive, irreversible loss of peripheral vision
 - paracentral defects, arcuate scotoma and nasal step are characteristic
 - late loss of central vision if untreated

Treatment

- medical treatment: decrease IOP by increasing the drainage and/or decreasing the production of aqueous (see *Glaucoma Medications*, Table 10, OP45)
 - increase aqueous outflow
 - ♦ topical cholinergics
 - ♦ topical prostaglandin analogues
 - ♦ topical alpha-adrenergics
 - decrease aqueous production
 - ♦ topical beta-blockers
 - ♦ topical and oral carbonic anhydrase inhibitor
 - ♦ topical alpha-adrenergics
- laser trabeculoplasty, cyclophotocoagulation = selective destruction of ciliary body (for refractory cases)
- trabeculectomy (see *Surgical Ophthalmology*, OP43)
- optic nerve head examination, IOP measurement and visual field testing to monitor course of disease
- pachymetry to measure corneal thickness

Normal Pressure Glaucoma

- POAG with IOP in normal range
- often found in women >60 but may occur earlier
- damage to optic nerve may be due to vascular insufficiency

Treatment

- treat any causative underlying medical condition and lower the IOP further

Secondary Open Angle Glaucoma

- increased IOP secondary to ocular/systemic disorders that clog the trabecular meshwork
 - steroid-induced glaucoma
 - traumatic glaucoma
 - pigmentary dispersion syndrome
 - pseudoexfoliation syndrome

Primary Angle Closure Glaucoma

- 5% of all glaucoma cases
- peripheral iris bows forward in an already susceptible eye with a shallow anterior chamber obstructing aqueous access to the trabecular meshwork
- sudden shifting forward of the lens-iris diaphragm = pupillary block, results in inability of the aqueous to flow from the posterior chamber to the anterior chamber and a sudden rise in IOP (Figure 20)

Risk Factors

- hyperopia: small eye, big lens – large lens crowds the angle
- age >70
- female
- family history
- more common in people of Asian and Inuit descent
- mature cataracts
- shallow anterior chamber
- pupil dilation (topical and systemic anticholinergics, stress, darkness)

Reduction of Intraocular Pressure and Glaucoma Progression

Arch Ophthalmol 2002; 120:1268-1279

Study: Randomized controlled clinical trial.

Patients: 255 participants, mainly selected through a population screening protocol, aged 50-80 with newly detected open-angle glaucoma, visual field defects, and a median intraocular pressure (IOP) of 20 mmHg.

Intervention: Participants were randomized to either topical beta-blocker (betaxolol) plus argon laser trabeculoplasty or no initial treatment, with close observation for both groups. Median follow-up was 6 years.

Main Outcome: Glaucoma progression as defined by visual field and optic disc abnormalities.

Results: IOP was reduced by 25% (mean 5.1 mmHg) in the treatment group. Glaucoma progression was evident in 62% of individuals in the control group vs. only 45% in the treatment group ($p=0.007$). The progression was significantly later in the treatment group vs. the controls.



Rule of Fours

1/4 of general population after using 4 weeks of topical steroid 4x/day will develop an increase in IOP.

Medical Interventions for Primary Open Angle Glaucoma and Ocular Hypertension

Cochrane Database of Systematic Reviews 2007, Issue 4.

Study: Cochrane systematic review of 26 trials and meta-analysis of 10 trials investigating the effectiveness of topical pharmacological therapies for primary open angle glaucoma (POAG) or ocular hypertension (OHT).

Patients: 4979 participants randomized in 26 trials. Patients had OHT with intraocular pressure (IOP) >21 mmHg or open angle glaucoma.

Intervention: topical eye medications, including beta-blockers, dorzolamide, brimonidine, pilocarpine and epinephrine versus each other and placebo.

Main outcome: Reduction of progression or prevention of onset of visual field defects.

Results: Meta-analysis on all trials that tested drugs against placebo or untreated controls demonstrated that lowering IOP reduces incidence of glaucomatous visual field defects, with an odds ratio of 0.62 (95% CI 0.47-0.81). However, this result is of limited practical use since different therapies were pooled. No single drug demonstrated significant visual field protection. However, as a class, beta-blockers showed borderline significance in reducing onset of glaucoma in patients with OHT when compared to placebo, with an OR of 0.67 (95% CI 0.45-1.00).

Conclusions: Lowering IOP can reduce progression of visual field defects in patients with OHT.

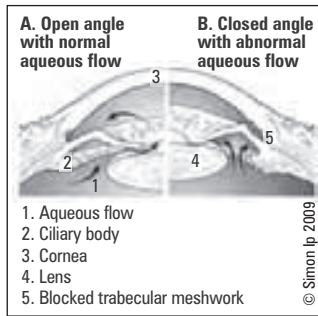


Figure 20. Normal Open Angle versus Angle Closure Glaucoma

Clinical Features

- unilateral, but other eye predisposed
- red, painful eye = **RED FLAG**
- decreased visual acuity, vision acutely blurred from corneal edema
- halos around lights
- nausea and vomiting, abdominal pain
- fixed, mid-dilated pupil
- corneal edema with conjunctival injection
- marked increase in IOP; may be noticeable even to palpation (>40 mmHg)
- shallow anterior chamber ± cells in anterior chamber

Complications

- irreversible loss of vision within hours to days if untreated
- permanent peripheral anterior synechiae

Treatment

- refer to ophthalmologist
 - laser iridotomy
 - aqueous suppressants and hyperosmotic agents
- immediate treatment important to:
 - preserve vision
 - prevent adhesions of peripheral iris to trabecular meshwork (peripheral anterior synechiae) resulting in permanent closure of angle
- medical treatment (see *Glaucoma Medications*, Table 10, OP45)
 - miotic drops (pilocarpine) to reverse pupillary block
 - decrease IOP
 - ♦ topical beta-blockers
 - ♦ topical adrenergics
 - ♦ topical cholinergics
 - pilocarpine 1-4% q15min, up to q5min
 - ♦ systemic carbonic anhydrase inhibitors
 - IV acetazolamide 250-500 mg
 - ♦ systemic hyperosmotic agents
 - oral glycerine 1 g/kg
 - IV mannitol 1 g/kg



Angle Closure Glaucoma

BACH

Tx with miotics and **B**eta-Blockers,
Adrenergics, **C**holinergics
Hyperosmotic agents

Secondary Angle Closure Glaucoma

Uveitis

- inflamed iris adheres to lens (posterior synechiae)

Neovascular Glaucoma

- abnormal blood vessels develop on surface of iris (rubeosis iridis), in the angle, and within the trabecular meshwork
- due to retinal ischemia associated with proliferative diabetic retinopathy and CRVO
- treatment with laser therapy to retina reduces neovascular stimulus to iris vessels

Pupils

- pupil size is determined by the balance between the sphincter muscle and the dilator muscle
- sphincter muscle is innervated by the parasympathetic nervous system (PNS)
 - carried by CN III: pre- and post-ganglionic fibres synapse in ciliary ganglion, and use acetylcholine as the neurotransmitter
- dilator muscle is innervated by the sympathetic nervous system (SNS)
 - first order neuron = hypothalamus → brainstem → spinal cord
 - second order/pre-ganglionic neuron = spinal cord → sympathetic trunk via internal carotid artery → superior cervical ganglion in neck
 - third order/post-ganglionic fibres originate in the superior cervical ganglion, neurotransmitter is noradrenaline
 - ♦ as a diagnostic test, 4% cocaine prevents the re-uptake of noradrenaline, and will cause dilation of normal pupil, but not one with loss of sympathetic innervation (Horner's Syndrome)



5 Targets of Retinal Signals

- Pre-tectal nucleus (pupillary reflex/eye movements)
- Lateral geniculate body of thalamus
- Superior colliculus (eye movements)
- Suprachiasmatic nucleus (optokinetic)
- Accessory optic system (circadian rhythm)

Pupillary Light Reflex

- light shone directly into eye travels along optic nerve → optic tracts → both sides of midbrain
- impulses enter both sides of midbrain via pretectal area and Edinger-Westphal nuclei
- nerve impulses then travel down CN III bilaterally to reach the ciliary ganglia, and finally to the iris sphincter muscle, which results in direct and consensual light reflex

Pupil Abnormalities



Denervation Hypersensitivity

- when post-ganglionic fibres are damaged, the understimulated end-organ develops an excess of receptor and becomes hypersensitive
- postganglionic parasympathetic lesions (i.e. Adie's pupil)
 - pupil will constrict with 0.125% pilocarpine (cholinergic agonist), normal pupil will not
- postganglionic sympathetic lesions (this test is used to differentiate between pre- and post-ganglionic lesions in Horner's syndrome)
 - pupil will dilate with 0.125% adrenaline, normal pupil will not

Local Disorders of Iris

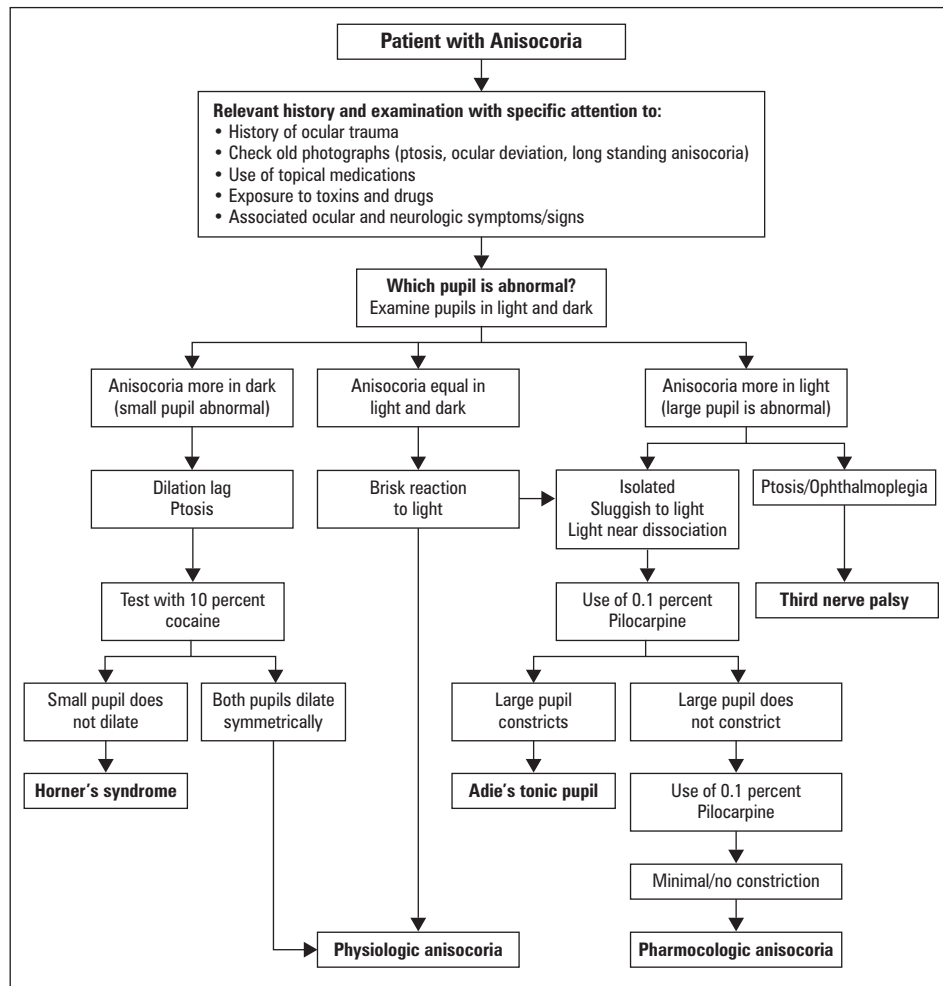
- posterior synechiae (adhesions between iris and lens) due to iritis can present as an abnormally shaped pupil
- ischemic damage [e.g. post-acute angle-closure glaucoma (ACG)]
 - ischemic damage usually at 3 and 9 o'clock positions result in a vertically oval pupil that reacts poorly to light
- trauma (e.g. post intraocular surgery)

Anisocoria

- unequal pupil size
- idiopathic/physiologic anisocoria
 - 20% of population
 - round, regular, <1 mm difference
 - pupils reactive to light and accommodation
 - responds normally to mydriatics/miotics
- see Table 6 for other causes of anisocoria

Table 6. Summary of Conditions Causing Anisocoria

	Features	Site of Lesion	Light and Accommodation	Anisocoria	Mydriatics/Miotics	Effect of Pilocarpine
ABNORMAL MIOTIC PUPIL (impaired pupillary dilation)						
Argyll-Robertson Pupil	Irregular, usually bilateral	Midbrain	Poor to light; better to accommodation		Dilates/Constricts	
Horner's Syndrome	Round, unilateral, ptosis, anhidrosis, pseudoenophthalmos	Sympathetic system	Both brisk	Greater in dark	Dilates/Constricts	
ABNORMAL MYDRIATIC PUPIL (impaired pupillary constriction)						
Adie's Tonic Pupil	Irregular, larger in bright light	Ciliary ganglion	Poor to light, better to accommodation	Greater in light	Dilates/Constricts	Constricts (hypersensitivity to dilute pilocarpine)
CN III Palsy	Round	CN III	± fixed (acutely) at 7-9 mm	Greater in light	Dilates/Constricts	Constricts
Mydriatic Pupil	Round, uni- or bilateral	Iris sphincter	Fixed at 7-8 mm	Greater in light	No effect	Will not constrict

**Figure 21. Approach to Anisocoria**

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Dilated Pupil (Mydriasis)

Sympathetic Stimulation

- fight or flight response
- mydriatic drugs: epinephrine, dipivefrin (Propine®), phenylephrine

Parasympathetic Understimulation

- cycloplegics/mydriatics: atropine, tropicamide, cyclopentolate (parasympatholytic)
- CN III palsy
 - eye deviated down and out with ptosis present
 - etiology includes stroke, neoplasm, aneurysm, acute rise in ICP, diabetes mellitus (may spare pupil), trauma
 - CN III palsy will respond to drugs (e.g. pilocarpine), unlike a pupil dilated from medication (mydriatics)

Acute Angle Closure Glaucoma

- fixed, mid-dilated pupil

Adie's Tonic Pupil

- 80% unilateral, females > males
- pupil is tonic or reacts poorly to light (both direct and consensual) but constricts with accommodation
- if decreased deep tendon reflexes = Adie's syndrome
- caused by benign lesion in ciliary ganglion; results in denervation hypersensitivity of parasympathetically innervated constrictor muscle
 - dilute (0.125%) solution of pilocarpine will constrict tonic pupil but have no effect on normal pupil
- pupil eventually gets smaller than pupil of unaffected eye



In a CN III palsy, if the pupil is involved, consider the possibility of a posterior communicating artery aneurysm. The pupillomotor fibers run on the outside of the nerve and are most susceptible to compression. Ischemic changes are more likely to cause a palsy without pupillary involvement.

Trauma

- damage to iris sphincter from blunt or penetrating trauma
- iris transillumination defects may be apparent using ophthalmoscope or slit lamp
- pupil may be dilated (traumatic mydriasis) or irregularly shaped from tiny sphincter ruptures

Constricted Pupil (Miosis)**Senile Miosis**

- decreased sympathetic stimulation with age

Parasympathetic Stimulation

- local or systemic medications such as:
 - cholinergic agents: pilocarpine, carbachol
 - cholinesterase inhibitor: phospholine iodide
 - opiates, barbiturates

Horner's Syndrome

- see Neurology, N24
- lesion in sympathetic pathway
- difference in pupil size greater in dim light, due to decreased innervation of adrenergics to iris dilator muscle
- associated with ptosis, anhidrosis of ipsilateral face/neck
- application of cocaine 4% (blocks reuptake of noradrenaline) to eye does not result in pupil dilation (vs. physiologic anisocoria)
- hydroxyamphetamine 1% (stimulates noradrenaline release) will dilate pupil if central or preganglionic lesion, not postganglionic lesion
- postganglionic lesions result in denervation hypersensitivity, which will cause pupil to dilate with 0.125% adrenaline, whereas normal pupil will not
- causes: carotid or subclavian aneurysm, brainstem infarct, demyelinating disease, cervical or mediastinal tumour, Pancoast tumour, goiter, cervical lymphadenopathy, surgical sympathectomy, Lyme disease, cervical ribs, tabes dorsalis, cervical vertebral fractures



Horner's MAP
Miosis
Anhidrosis
Ptosis

Iritis

- miotic pupil initially
- later, may be irregularly shaped pupil due to posterior synechiae
- later stages non-reactive to light

Argyll Robertson Pupil

- both pupils irregular and <3 mm in diameter, ± ptosis
- does not respond to light stimulation
- responds to accommodation (light-near dissociation)
- suggestive of CNS syphilis or other conditions (DM, encephalitis, MS, chronic alcoholism, CNS degenerative diseases)



Argyll Robertson Pupil (ARP)
Accommodation Reflex Present
Pupillary Reflex Absent

Relative Afferent Pupillary Defect (RAPD)

- see Neurology, N23
- also known as Marcus Gunn pupil
- lesion in visual afferent (sensory) pathway anterior to optic chiasm
- DDX: large retinal detachment, BRAO, CRAO, CRVO, advanced glaucoma, optic nerve compression, optic neuritis
- does not occur with media opacity (e.g. corneal edema, cataracts)
- test: swinging flashlight
 - if light is shone in the affected eye, direct and consensual response to light is decreased
 - if light is shone in the unaffected eye, direct and consensual response to light is normal
 - if the light is moved quickly from the unaffected eye to the affected eye, "paradoxical" dilation of both pupils occurs
 - observe red reflex, especially in patients with dark iris



Cataracts never produce a RAPD.



It is possible to have RAPD and normal vision at the same time.
i.e. in damaged superior colliculus caused by thalamic hemorrhage.



When assessing for an RAPD, a slight dilatation after initial constriction is normal when swinging from eye to eye.

Malignancies

- uncommon site for primary malignancies
- eye usually affected secondarily by cancer or cancer treatments
- see *Retinoblastoma* section, OP41



Lid Carcinoma

Etiology

- basal cell carcinoma (90%)
 - spread via local invasion, rarely metastasizes
 - rodent ulcer, indurated base with pearly rolled edges, telangiectasia
- squamous cell carcinoma (<5%)
 - spread via local invasion, may also spread to nodes and metastasize
 - ulceration, keratosis of lesion
- sebaceous cell carcinoma (1-5%)
 - often masquerades as chronic blepharitis or recurrent chalazion
 - highly invasive, metastasize
- Kaposi's sarcoma, malignant melanoma, Merkel cell tumour, metastatic tumour

Treatment

- incisional or excisional biopsies
- may require cryotherapy, radiotherapy, chemotherapy, immunotherapy
- surgical reconstruction

Malignant Melanoma

- most common **primary** intraocular malignancy in adults
- more prevalent in Caucasians
- arise from uveal tract
- hepatic metastases predominate

Treatment

- choice is dependent on the size of the tumour
- radiotherapy, enucleation (removal of globe from eye socket), limited surgery

Metastases

- most common intraocular malignancy in adults
- most commonly from breast and lung in adults, neuroblastoma in children
- usually infiltrate the choroid, but may also affect the optic nerve or extraocular muscles
- may present with decreased or distorted vision, irregularly shaped pupil, iritis, hyphema

Treatment

- local radiation, chemotherapy
- enucleation if blind, painful eye

Ocular Manifestations of Systemic Disease

HIV/AIDS

- up to 75% of patients with AIDS have ocular manifestations

External ocular signs

- Kaposi's sarcoma
 - affects conjunctiva of lid or globe
 - numerous vascular skin malignancies
 - DDx: subconjunctival hemorrhage (non-clearing), hemangioma
- multiple molluscum contagiosum
- herpes simplex keratitis
- herpes zoster keratitis

Retina

- HIV retinopathy (most common)
 - cotton wool spots in >50% of HIV
 - intraretinal hemorrhage
- cytomegalovirus (CMV) retinitis
 - ocular opportunistic infection that develops in late stages of HIV when severely immunocompromised (CD4 count ≤ 50)
 - a necrotizing retinitis, with retinal hemorrhage and vasculitis, “brushfire” or “pizza pie” appearance
 - symptoms and signs: scotomas (macular involvement and retinal detachment), blurred vision and floaters
 - untreated infection will progress to other eye in 4-6 weeks
 - treatment: virostatic agents, e.g. gancyclovir or foscarnet via IV or intravitreal injection
- necrotizing retinitis
 - from herpes simplex virus, herpes zoster, toxoplasmosis
- disseminated choroiditis
 - *Pneumocystis carinii*, *Mycobacterium avium intracellulare*, *Candida*



Other Systemic Infections

- herpes zoster
 - see *Herpes Zoster Keratitis* section, OP19
- candidal endophthalmitis
 - fluffy, white-yellow, superficial retinal infiltrate that may eventually result in vitritis
 - may present with inflammation of the anterior chamber
 - treatment: systemic amphotericin B, oral fluconazole
- toxoplasmosis
 - focal, grey-yellow-white, chorioretinal lesions with surrounding vasculitis and vitreous infiltration (vitreous cells)
 - can be congenital (transplacental) or acquired (caused by *Toxoplasma gondii* protozoa transmitted through raw meat and cat feces)
 - congenital form more often visual impairing as more likely to involve macula
 - treatment: pyrimethamine, sulfonamide, folinic acid, or clindamycin. Consider steroids if severe inflammation (vitritis, macular or optic nerve involvement)

Diabetes Mellitus (DM)



- see *Endocrinology*, E6
- most common cause of blindness in young people in North America
- consider DM if unexplained retinopathy, cataract, EOM palsy, optic neuropathy, sudden change in refractive error
- loss of vision due to:
 - progressive microangiopathy leading to macular edema
 - progressive diabetic retinopathy \rightarrow neovascularization \rightarrow traction \rightarrow retinal detachment and vitreous hemorrhage
 - rubeosis iridis (neovascularization of the iris) leading to neovascular glaucoma (poor prognosis)
 - macular ischemia



Macular edema is the most common cause of visual loss in patients with background DR.

DIABETIC RETINOPATHY (DR)**Background**

- altered vascular permeability (loss of pericytes, breakdown of blood-retinal barrier, thickening of basement membrane)
- retinal vessel closure

Classification

- **non-proliferative:** increased vascular permeability and retinal ischemia
 - dot and blot hemorrhages
 - microaneurysms
 - hard exudates (lipid deposits)
 - macular edema
- **advanced non-proliferative (or pre-proliferative):**
 - non-proliferative findings plus:
 - ♦ venous beading (in ≥ 2 of 4 retinal quadrants)
 - ♦ intraretinal microvascular anomalies (IRMA) in 1 of 4 retinal quadrants
 - IRMA: dilated, leaky vessels within the retina
 - ♦ cotton wool spots (nerve fibre layer infarcts)

**Presence of DR in:****Type 1 DM**

25% after 5 years
60% after 10 years
>80% after 15 years

Type 2 DM

20% at time of diagnosis
60% after 20 years



Clinically significant macular edema is defined as thickening of the retina at or within 500 μm of the centre of the macula.

- **proliferative**
 - 5% of patients with diabetes will reach this stage
 - neovascularization of iris, disc, retina to vitreous
 - ♦ neovascularization of iris (rubeosis iridis) can lead to neovascular glaucoma
 - ♦ vitreous hemorrhage from bleeding, fragile new vessels, fibrous tissue can contract causing tractional retinal detachment
 - high risk of severe visual loss 2° to vitreous hemorrhage, retinal detachment

Screening Guidelines for Diabetic Retinopathy

- Type 1 DM
 - screen for retinopathy beginning annually 5 years after disease onset
 - screening not indicated before the onset of puberty
- Type 2 DM
 - initial examination at time of diagnosis, then annually
- pregnancy
 - ocular exam in 1st trimester, close follow-up throughout as pregnancy can exacerbate DR
 - gestational diabetics not at risk for retinopathy

Diabetic Control and Complication Trial *NEJM* 1993; 329(14)

DCCT trial shows intensive glycemic control will reduce the risk of diabetic retinopathy by 76%, and reduce the risk of worsening diabetic retinopathy by 54%.

Early Treatment Diabetic Retinopathy Study

Early Treatment Diabetic Retinopathy Study
Investigators: Aspirin effects on mortality and morbidity in patients with diabetes mellitus. *ETDRS Report 14. JAMA* 1992; 268:1292-1300. And other publications by the same group

ETDRS Demonstrates

- No benefit of aspirin in reduction in risk of progression of diabetic retinopathy, however no increased risk of hemorrhage either
- Early treatment using panretinal photocoagulation reduces the risk of visual loss
- Clinically significant macula edema should be treated by focal laser

Treatment

- Diabetic Control and Complications Trial (DCCT)
 - tight control of blood sugar decreases frequency and severity of microvascular complications
- blood pressure control
- focal laser for clinically significant macular edema
- panretinal laser photocoagulation for proliferative diabetic retinopathy: reduces neovascularization, hence reducing the angiogenic stimulus from ischemic retina by decreasing retinal metabolic demand → reduces risk of blindness
- vitrectomy for non-clearing vitreous hemorrhage and retinal detachment in proliferative diabetic retinopathy
- vitrectomy before vitreous hemorrhage does not improve the visual prognosis

Lens Changes

- earlier onset of senile nuclear sclerosis and cortical cataract
- may get hyperglycemic cataract, due to sorbitol accumulation (rare)
- changes in blood glucose levels (poor control) can suddenly cause refractive changes by 3-4 diopters

Extra Ocular Muscle (EOM) Palsy

- usually CN III infarct
- pupil usually spared in diabetic CN III palsy, but get ptosis
- may involve CN IV and VI
- usually recover within few months

Optic Neuropathy

- visual acuity loss due to infarction of optic disc/nerve

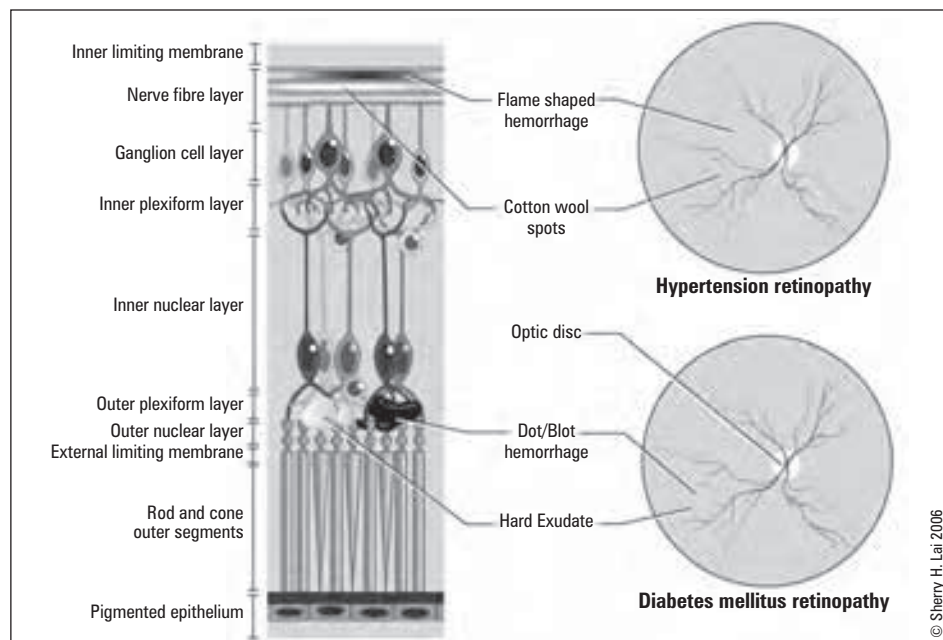


Figure 22. DM vs. HTN Retinopathy

Hypertension

- retinopathy is the most common ocular manifestation
- key features of **chronic** HTN retinopathy: AV nicking, blot retinal hemorrhages, microaneurysms, cotton wool spots
- key features of **acute** HTN retinopathy: retinal arteriolar spasm, superficial retinal hemorrhage, cotton wool spots, optic disc edema

Table 7. Keith-Wagener-Barker Classification

Group 1	Mild arterial narrowing
Group 2	Obvious arterial narrowing with focal irregularities
Group 3	Group 2 plus Cotton-wool spots Hemorrhage and/or exudate
Group 4	Group 3 plus papilledema

Multiple Sclerosis (MS)

- see [Neurology](#), N49

Clinical Features

- blurred vision and decreased colour vision: 2° to optic neuritis
- central scotoma: due to damage to papillomacular bundle of retinal nerve fibres
- diplopia: 2° to internuclear ophthalmoplegia (INO)
- RAPD, ptosis, nystagmus, uveitis, optic atrophy, optic neuritis
- white matter demyelinating lesions of optic nerve on MRI

Treatment

- IV steroids with taper to oral form for optic neuritis
 - NOT oral steroids in isolation as this increases likelihood of developing MS later

Optic Neuritis Treatment Trial (ONTT)
Optic Neuritis Study Group: The Optic Neuritis Treatment Trial. Three-year follow-up results.
Arch Ophthalmol 1995; 113:136-137
 ONTT recruited patients with acute new onset optic neuritis and studied outcome of three treatment regimens: oral steroid x 14d, IV steroid x 3d + oral steroid x 11d, and placebo x 14d. They found that oral steroid actually increases risk of recurrence, IV + oral steroid expedite recovery, and "no treatment" a viable therapeutic option. IV + oral steroid does not decrease risk of recurrence. Furthermore, brain MRI is most valuable in prediction of onset of MS.

TIA/Amaurosis Fugax

- sudden, transient blindness from intermittent vascular compromise; ipsilateral carotid most frequent embolic source
- typically monocular, lasting <5-10 minutes
- Hollenhorst plaques (glistening microemboli seen at branch points of retinal arterioles)

Graves' Disease

- ophthalmopathy occurs despite control of thyroid gland status
- ocular manifestations occur secondary to sympathetic overdrive and/or specific inflammatory infiltrate of the orbital tissue

Clinical

- initial inflammatory phase is followed by a quiescent cicatricial phase

Treatment

- treat hyperthyroidism
- monitor for corneal exposure and maintain corneal hydration
- manage diplopia, proptosis and compressive optic neuropathy with one or a combination of:
 - steroids (during acute phase)
 - orbital bony decompression
 - external beam radiation of the orbit
- consider strabismus and/or eyelid surgical procedures once acute phase subsides



The most common cause of unilateral or bilateral proptosis in adults is Graves' disease.



Progression of Signs and Symptoms of Graves' Ophthalmopathy

NO SPECS

No signs/symptoms
 Only signs (lid retraction, lid lag)
 Soft tissue swelling (periorbital edema)
 Proptosis (exophthalmos)
 Extraocular muscle weakness (causing diplopia)
 Corneal exposure
 Sight loss

Connective Tissue Disorders

- RA, juvenile idiopathic arthritis (JIA), SLE, Sjogren's syndrome, ankylosing spondylitis, polyarteritis nodosa (PAN)
- most common ocular manifestation: dry eyes (keratoconjunctivitis sicca)

**ESR in GCA**

Males > age/2

Females > (age + 10) / 2

Does this Patient have GCA?

JAMA 2002; 287:92-101

Rule in: jaw claudication and diplopia on history, temporal artery beading, prominence of the artery and tenderness over the artery on exam.

Rule out: no temporal artery abnormalities on exam, normal ESR.

Giant Cell/Temporal Arteritis (GCA)

- see [Rheumatology](#), R17

Clinical

- more common in women >60 y.o.
- abrupt monocular loss of vision, pain over the temporal artery, jaw claudication, scalp tenderness, polymyalgia rheumatica, and constitutional symptoms
- ischemic optic atrophy
 - 50% lose vision in other eye if untreated

Diagnosis

- temporal arterial biopsy + increased ESR (ESR can be normal, but likely 80-100 in first hour), CRP
- if biopsy of one side is negative, biopsy the other side

Treatment

- high dose corticosteroid to relieve pain and prevent further ischemic episodes
- if diagnosis of GCA is suspected clinically: start treatment + perform temporal artery biopsy to confirm diagnosis within 2 weeks of initial presentation (DO NOT WAIT TO TREAT)

Sarcoidosis

- granulomatous uveitis with large “mutton fat” keratic precipitates and posterior synechiae
- neurosarcoidosis: optic neuropathy, oculomotor abnormalities, visual field loss

Treatment

- steroids and mydriatics

Pediatric Ophthalmology

Strabismus

- ocular misalignment, found in 3% of children
- object not visualized simultaneously by fovea of each eye
- often presents with parental concern about a wandering eye, crossing eye, or poor vision
- types: heterotropia (paralytic or non-paralytic), heterophoria
- distinguish from pseudostrabismus (prominent epicanthal folds, hypertelorism)
- complications: amblyopia, cosmesis

HETEROTROPIA

- manifest deviation
- deviation not corrected by the fusion mechanism (i.e. deviation is apparent when the patient is using both eyes)

Types

- exo- (lateral deviation), eso- (medial deviation)
- hyper- (upward deviation), hypo- (downward deviation)
- esotropia = “crossed-eyes”; exotropia = “wall-eyed”
- pseudoesotropia: epicanthal folds give appearance of esotropia but Hirschberg test is normal, more common in Asians

Tests

- Hirschberg test (corneal light reflex): positive if the light reflex in the cornea of the two eyes is asymmetrical
 - light reflex lateral to central cornea indicates esodeviation; light reflex medial to central cornea indicates exodeviation
 - false positives occur if visual axis and anatomic pupillary axis of the eye are not aligned (angle kappa)
- cover test (Figure 23)
 - ask patient to fixate on target
 - cover the fixating eye, the deviated eye will then move to fixate on the target
 - if deviated eye moves inward = exotropia
 - if deviated eye moves outward = esotropia
- the deviation can be quantified using prisms

HETEROPHORIA

- latent deviation
- deviation corrected in the binocular state by the fusion mechanism (i.e. deviation not seen when patient is using both eyes)
- Hirschberg test will be normal (light reflexes symmetrical)
- very common – majority are asymptomatic
- may be exacerbated or become manifest with asthenopia (eye strain, fatigue)

Tests

- cover-uncover test (Figure 23)
 - placing a cover over an eye with a phoria causes a breakdown of fixation of that eye, which allows it to move to a misaligned position
 - uncovering the covered eye will allow it to return to a normal central position
 - covered eye moves inward on removing cover = exophoria
 - covered eye moves outward on removing cover = esophoria
- alternate cover test
 - alternating the cover between both eyes reveals the total deviation, both latent and manifest
 - maintain cover over one eye for 2-3 seconds before rapidly shifting to other eye

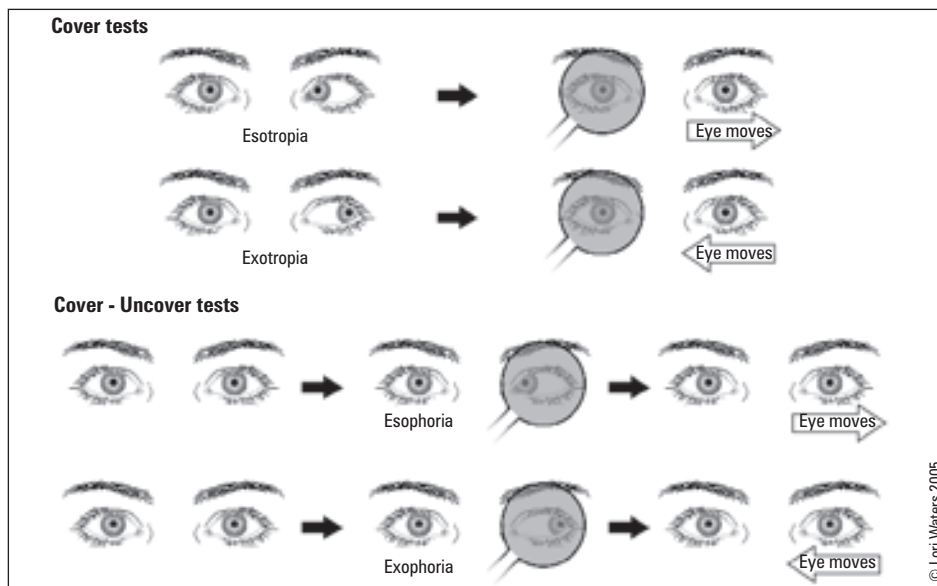


Figure 23. Cover and Cover-Uncover Tests for Detection of Tropias and Phorias

PARALYTIC STRABISMUS

- incomitant strabismus (i.e. deviation varies in different positions of gaze)
- reduction or restriction in range of eye movements

Etiology

- neural (CN III, IV, VI): ischemia (e.g. DM), MS, aneurysm, brain tumour, trauma
- muscular: myasthenia gravis (neuromuscular junction pathology), Graves' disease
- structural: restriction/entrapment of extraocular muscles due to orbital inflammation, tumour, fracture of the orbital wall

Clinical Features

- mostly in adults, acquired
- present mainly with diplopia
- greatest deviation in field of action of the weakened muscle
- visual acuity is usually unaffected in either eye, unless CN II is involved

NON-PARALYTIC STRABISMUS

- concomitant strabismus (i.e. deviation equal in all directions of gaze)
- no restriction in range of eye movements
- monocular, alternating, or intermittent

Clinical Features

- usually begins in infancy, up to age 8-10
- usually no diplopia (child suppresses the image from the misaligned eye)
- deviated eye may become amblyopic if not treated when the child is young. Amblyopia treatment rarely successful after age 8-10 (see *Amblyopia*, OP39)
- amblyopia usually does not develop if child has alternating strabismus or intermittency – allows neural pathways for both eyes to develop



All children with strabismus and/or possible reduced vision require prompt referral to an ophthalmologist.

Accommodative Esotropia

- normal response to approaching object is the triad of the near reflex: convergence, accommodation and miosis
- hyperopes must constantly accommodate – excessive accommodation can lead to esotropia in young children via over-activation of the near reflex
- average age of onset is 2.5 years
- usually reversible with correction of refractive error

Non-accommodative Esotropia

- accounts for 50% of childhood strabismus
- most are idiopathic
- may be due to monocular visual impairment (e.g. cataract, corneal scarring, anisometropia, retinoblastoma) or divergence insufficiency (ocular misalignment that is greater at distance fixation than at near fixation)

Amblyopia

Definition

- reduction of best corrected visual acuity due to cortical suppression of sensory input from an eye that is receiving blurred or conflicting visual information, leading to disruption of the normal development of visual pathways serving that eye

Detection

- “Holler Test”: young child upset if good eye is covered
- quantitative visual acuity by age 3-4 years using picture charts and/or matching game (Sheridan-Gardiner), testing each eye separately
- amblyopia treatment less successful after age 8-10 years, but a trial should be given no matter what age
- prognosis: 90% will have good vision restored and maintained if treated <4 years old

Etiology and Management

- **strabismus**
 - correct with glasses for accommodative esotropia (50% of children experience relief of their esotropia with glasses and will not require surgery)
 - occlusion of unaffected eye forces brain to use previously strabismic eye; aims to bring vision in previously suppressed eye to normal before surgery
 - surgery: recession (weakening) = moving muscle insertion further back on the globe; or resection (strengthening) = shortening the muscle
 - botulinum toxin for single muscle weakening
 - after ocular alignment is restored (glasses, surgery, botulinum toxin), patching is frequently necessary to maintain vision until approximately age 8
- **refractive errors**
 - anisometropia (difference in refractive power between the eyes)
 - amblyopia usually in the more hyperopic eye
 - the less hyperopic eye receives a clear image while the more hyperopic eye receives a blurred image; input from the blurred eye is cortically suppressed and visual pathway fails to develop normally
 - treat with glasses to correct refractive error
 - patching is required if visual acuity difference persists after 4-8 weeks of using glasses
- **deprivation amblyopia**
 - occlusion due to ptosis, cataract, retinoblastoma, corneal opacity
 - occlusion amblyopia: prolonged patching of good eye may cause it to become amblyopic

General Treatment

- correct the underlying cause
- occlusion therapy (patching) or atropine cycloplegia (optical degradation therapy) of the good eye

Leukocoria

- white pupil (red reflex is absent)

Differential Diagnosis

- cataract
- retinoblastoma
- retinal coloboma
- retinopathy of prematurity (ROP)
- persistent hyperplastic primary vitreous (PHPV)
- Coat's disease (exudative retinitis)
- toxocariasis
- retinal detachment

Retinoblastoma

- most common primary intraocular malignancy in children
- incidence: 1/1000; sporadic or genetic transmission; screening of siblings/offspring essential
- unilateral or bilateral (in 1/3 of cases)
- malignant – direct or hematogenous spread
- diagnosis
 - may be detected by leukocoria in infant
 - CT scan: dense radiopaque appearance (contains calcium)

Treatment

- radiotherapy, chemotherapy combined with laser, cryopexy, and/or enucleation

Retinopathy of Prematurity (ROP)

- vasoproliferative retinopathy that is a major cause of blindness in the developed world

Risk Factors

- non-black race (black infants have lower risk of developing ROP)
- low gestational age, birth weight (<1500 g)
- high oxygen exposure after birth

Classification

- Stage 1: faint demarcation line at the junction between the vascularized and avascular retina
- Stage 2: elevated ridge
- Stage 3: extra-retinal fibrovascular tissue extending into uterine
- Stage 4: partial retinal detachment (4A: macula “on”, 4B: macula “off”)
- Stage 5: total retinal detachment
- Plus (+) disease = dilatation and tortuosity of retinal vessels
- threshold disease: stage 3+ in zones 1 or 2 with 5 continuous or 8 cumulative clock hours of ROP involvement (Figure 24)

Treatment

- threshold disease is treated with cryotherapy or laser (laser is now the standard treatment, with better refractive outcome)
- ROP beyond threshold level is either watched carefully (usually stage 4A) or treated with vitrectomy/scleral buckle

Prognosis

- higher incidence of myopia among ROP infants, even if treated successfully
- stage 4B and 5 have poor prognosis for visual outcome despite treatment

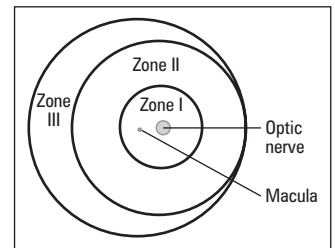


Figure 24. Zones of the Retina in ROP

Nasolacrimal System Defects

- congenital obstruction of the nasolacrimal duct (failure of canalization), usually occurs at 1-2 months of age
- increased tearing, crusting, discharge, recurrent conjunctivitis
- can have reflux of mucopurulent material from lacrimal punctum when pressure is applied over lacrimal sac
- treatment: massage over lacrimal sac at medial corner of eyelid
- consider referral for duct probing if no spontaneous resolution after 9-12 months

Ophthalmia Neonatorum

- newborn conjunctivitis in first month of life
- causes:
 - toxic: silver nitrate, erythromycin
 - infectious: bacterial (e.g. *N. gonorrhoeae* – most common, *Chlamydia trachomatis*), herpes simplex virus (HSV)
 - gonococcal infection is the most serious threat to sight as it can rapidly penetrate corneal epithelium, causing corneal ulceration
- diagnose using stains and cultures
- treatment: systemic antibiotics with possible hospitalization if infectious etiology
- topical prophylaxis, most commonly with erythromycin (or silver nitrate), is required by law at birth

Congenital Glaucoma

- due to inadequate development of the filtering mechanism of the anterior chamber angle

Clinical Features

- cloudy cornea, increased IOP
- photophobia, tearing
- buphthalmos (large “ox eye”), blepharospasm

Treatment

- filtration surgery is required soon after birth to prevent blindness

Ocular Trauma

Blunt Trauma

- caused by blunt object such as fist, squash ball
- history: injury, ocular history, drug allergy, tetanus status
- exam: VA first, pupil size and reaction, EOM (diplopia), external and slit lamp exam, ophthalmoscopy
- if VA normal or slightly reduced, globe less likely to be perforated
- if VA reduced may be perforated globe, corneal abrasion, lens dislocation, retinal tear
- bone fractures
 - blow out fracture: restricted EOM, diplopia, enophthalmos (sunken eye)
 - ethmoid fracture: subcutaneous emphysema of lid
- lids: swelling, laceration, emphysema
- conjunctiva: subconjunctival hemorrhage
- cornea: abrasion – detect with fluorescein staining and cobalt blue filter using slit lamp or ophthalmoscope
- anterior chamber: assess depth, hyphema, hypopyon
- iris: prolapse, iritis
- lens: cataract, dislocation
- retinal tear/detachment



Always test visual acuity (VA) first – medicolegal protection.



Refer if you observe any of these signs

- Decreased VA
- Shallow anterior chamber
- Hyphema
- Abnormal pupil
- Ocular misalignment
- Retinal damage



Management of Suspected Globe Rupture

CAN'T forget

CT orbits

Ancef IV

NPO

Tetanus status

Penetrating Trauma

- include ruptured globe ± prolapsed iris, intraocular foreign body
- rule out intraocular foreign body, especially if history of “metal striking metal”, orbit CT
- initial management: refer immediately!!
 - ABCs
 - don't press on eyeball!
 - don't check IOP if possibility of globe rupture
 - check vision, diplopia
 - apply rigid eye shield to minimize further trauma
 - keep head elevated 30-45° to keep IOP down
 - keep NPO
 - tetanus status
 - give IV antibiotics

Hyphema

- blood in anterior chamber often due to damage to root of the iris
- may occur with blunt trauma

Treatment

- refer to ophthalmology
 - shield and bedrest x 5 days or as determined by ophthalmologist
 - sleep with head upright
- may need surgical drainage if hyphema persists or if re-bleed

Complications

- risk of re-bleed highest on days 2-5, resulting in secondary glaucoma, corneal staining, and iris necrosis
- never prescribe aspirin, as it increases the risk of a re-bleed



Shaken Baby Syndrome

Syndrome of findings characterized by no external signs of abuse and respiratory arrest, seizures, and coma. Ocular exam findings are important diagnostically for Shaken Baby Syndrome. These findings include extensive retinal and vitreous hemorrhages that occur during the shaking process and are extremely rare in accidental trauma. A detailed fundoscopic exam or an ophthalmology referral should be conducted for all infants in whom abuse is suspected.

Blow-Out Fracture

- see Plastic Surgery, PL30
- blunt trauma causing fracture of orbital floor and herniation of orbital contents into maxillary sinus
- orbital rim remains intact
- inferior rectus and/or inferior oblique muscles may be incarcerated at fracture site
- infraorbital nerve courses along the floor of the orbit and may be damaged

Clinical Features

- pain and nausea at time of injury
- diplopia, restriction of EOM
- infraorbital and upper lip paresthesia (CN V₂)
- enophthalmos (sunken eye), periorbital ecchymoses

Investigations

- plain films: Waters' view and lateral
- CT: anteroposterior and coronal view of orbits

Treatment

- refrain from coughing, blowing nose
- systemic antibiotics may be indicated
- surgery if fracture >50% orbital floor, diplopia not improving, or enophthalmos >2 mm
- may delay surgery if the diplopia improves



Classic Signs of Blow-Out

Enophthalmos
Decreased upgaze (IR trapped)
Cheek anesthetized (infraorbital nerve trapped)

Chemical Burns

- alkali burns have a worse prognosis than acid burns because acids coagulate tissue and inhibit further corneal penetration
- poor prognosis if cornea opaque, likely irreversible stromal damage
- even with a clear cornea initially, alkali burns can progress for weeks (thus, very guarded prognosis)

Treatment

- irrigate at site of accident immediately with water or buffered solution
 - IV drip for at least 20-30 minutes with eyelids retracted in emergency department
 - swab upper and lower fornices to remove possible particulate matter
- do not attempt to neutralize because the heat produced by the reaction will damage the cornea
- cycloplegic drops to decrease iris spasm (pain) and prevent secondary glaucoma (due to posterior synechiae formation)
- topical antibiotics and patching
- topical steroids (by ophthalmologist) to decrease inflammation, use for less than two weeks (in the case of a persistent epithelial defect)



Fluorescein lights up alkali so you can detect it and assess whether it has been removed.

Surgical Ophthalmology

- **dacryocystorhinostomy (DCR)** – excision of bone covering the nasolacrimal sac to restore tear drainage
- **LASIK (laser-assisted in-situ keratomileusis)** – a microkeratome is used to create a corneal flap followed by laser remodeling of the stroma to correct refractive error
- **trabeculectomy** – creation of a new outflow tract from anterior chamber to under conjunctiva; fibrosis prevented with mitomycin C or 5-FU injection during surgery
- **phacoemulsification (cataract extraction)** – the use of ultrasonic waves to break up and aspirate a cataract followed by replacement with an artificial lens implant
- **vitrectomy** – the use of small trochars to enter the posterior segment and remove vitreous; commonly used to treat vitreous hemorrhage and retinal detachment
- **pneumatic retinopexy** – intraocular injection of air or an expandable gas in order to tamponade a retinal break
- **scleral buckle** – a band is secured on the outside of the globe that indents the eye wall, thereby relieving tension on the retina around any tears/holes and allowing the tears/holes to remain sealed

Ocular Drug Toxicity

Table 8. Drugs with Ocular Toxicity

Amiodarone	Corneal microdeposits and superficial keratopathy (vortex keratopathy) Rare: ischemic optic neuropathy
Atropine, benzotropine	Pupillary dilation (risk of angle closure glaucoma)
Bisphosphonates (Fosamax®, Actonel®)	Inflammatory eye disease (iritis, scleritis, episcleritis)
Chloroquine, hydroxychloroquine	Bull's eye maculopathy Vortex keratopathy
Chlorpromazine	Anterior subcapsular cataract
Contraceptive pills	Decreased tolerance to contact lenses Migraine Optic neuritis Central vein occlusion
Digitalis	Yellow vision Blurred vision
Ethambutol	Optic neuropathy
Haloperidol (Haldol®)	Oculogyric crises Blurred vision
Indomethacin	Superficial keratopathy
Interferon	Retinal hemorrhages and cotton wool spots
Isoniazid	Optic neuropathy
Nalidixic acid	Papilledema
Steroids	Posterior subcapsular cataracts Glaucoma Papilledema (systemic steroids) Increased severity of HSV infections (geographic ulcers) Predisposition to fungal infections
Sulphonamides, NSAIDS	Stevens-Johnson syndrome
Tamulosin (Flomax®)	Intraoperative Floppy Iris Syndrome (IFIS), which can complicate cataract surgery
Tetracycline	Papilledema (associated with pseudotumour cerebri)
Thioridazine	Pigmentary degeneration of retina
Vigabatrin	Retinal deposition with macular sparing, peripheral visual field loss
Vitamin A intoxication	Papilledema
Vitamin D intoxication	Band keratopathy

Common Medications

TOPICAL OCULAR DIAGNOSTIC DRUGS

Fluorescein Dye

- water soluble orange-yellow dye
- green under cobalt blue light (ophthalmoscope or slit lamp)
- absorbed in areas of epithelial loss (ulcer or abrasion)
- also stains mucus and contact lenses

Rose Bengal Stain

- stains devitalized epithelial cells and mucus

Anesthetics

- e.g. proparacaine HCl 0.5%, tetracaine 0.5%
- indications: removal of foreign body and sutures, tonometry, examination of painful cornea
- toxic to corneal epithelium (inhibit mitosis and migration) and can lead to corneal ulceration and scarring with prolonged use, therefore NEVER prescribe

Mydriatics

- dilate pupils
- two classes
 - cholinergic blocking (e.g. tropicamide [Mydracyl®])
 - ♦ dilation plus cycloplegia (lose accommodation) by paralysis of iris sphincter and the ciliary body
 - ♦ indications: refraction, ophthalmoscopy, therapy for iritis
 - adrenergic stimulating (e.g. phenylephrine HCl 2.5%)
 - ♦ stimulate pupillary dilator muscles, no effect on accommodation
 - ♦ usually used with tropicamide for additive effects
 - ♦ side effects: hypertension, tachycardia, arrhythmias

Table 9. Mydriatic Cycloplegic Drugs and Duration of Action

Drugs	Duration of Action
Tropicamide (Mydracyl®) 0.5%, 1%	4-5 hours
Cyclopentolate HCl 0.5%, 1%	3-6 hours
Homatropine HBr 1%, 2%	3-7 days
Atropine sulfate 0.5%, 1%	1-2 weeks
Scopolamine HBr 0.25%, 5%	1-2 weeks

GLAUCOMA MEDICATIONS**Table 10. Glaucoma Medications**

Drug Category	Dose	Effect	Comment/Side Effects
Alpha-Agonist Non-selective <ul style="list-style-type: none"> • epinephrine HCl 1% (Epifrin®) • dipivalyl epinephrine 0.1% (Propine®) Alpha₂-selective <ul style="list-style-type: none"> • brimonidine 0.2% (Alphagan®) • apraclonidine 0.5% (Lopidine®) 	1 gtt OS/OD bid/tid	1. Non-selective – ↓ aqueous production + ↑ TM outflow 2. Selective – ↓ aqueous production + ↑ uveoscleral outflow	1. Non-selective – mydriasis, macular edema, tachycardia 2. Selective – contact allergy, hypotension in children
Beta-Blocker Non-selective <ul style="list-style-type: none"> • timolol (Timoptic®) • levobunolol (Betagan®) Beta₁-selective <ul style="list-style-type: none"> • betaxolol (Betoptic®) 	1 gtt OS/OD qd/bid	↓ aqueous production	Bronchospasm (careful in asthma/COPD) ↑ CHF Bradycardia Hypotension Depression Heart block Impotence
Carbonic Anhydrase Inhibitor <ul style="list-style-type: none"> • dorzolamide (Trusopt®) • brinzolamide (Azopt®) • oral: acetazolamide (Diamox®) 	1 gtt OS/OD tid Diamox®: 500 mg PO bid	↓ aqueous production	**Must ask about sulfa allergy! Generally local side effects with topical preparations Oral: diuresis, fatigue, paresthesias, GI upset, etc.
Parasympathomimetic (cholinergic stimulating) <ul style="list-style-type: none"> • pilocarpine (Pilopine®) • carbachol (Isopto Carbachol®) 	1-2 gtts OS/OD tid/qid	↑ TM outflow	Miosis ↓ night vision ↑ GI motility Brow ache Headache ↓ heart rate
Prostaglandin Analogues <ul style="list-style-type: none"> • latanoprost (Xalatan®) • travaprost (Travatan®) • bimatoprost (Lumigan®) 	1 gtt OS/OD qhs	↑ uveoscleral outflow (uveoscleral responsible for 20% of drainage)	Iris colour change Periorbital skin pigmentation Lash growth Conjunctival hyperemia

Cosopt® = timolol + dorzolamide; Xalacom® = timolol + lantanoprost; Combigan® = timolol + brimonidine; DuoTrav® = timolol + travaprost
 gtt = drop, gtts = drops

WET AGE-RELATED MACULAR DEGENERATION MEDICATIONS**Vascular Endothelial Growth Factors (VEGF) Inhibitors**

- block vascular endothelial growth factor which prevents ocular angiogenesis and further development of choroidal neovascularization
- administered via intravitreal injections
- pegaptanib (Macugen®) is a selective anti-VEGF targeting VEGF isoform 165
- ranibizumab (Lucentis®) is a non-selective anti-VEGF agent
- bevacizumab (Avastin®) is another non-selective anti-VEGF agent but is only FDA approved for metastatic breast cancer, colorectal cancer and non-small cell lung cancer. Therefore, its use in ophthalmologic is off-label

TOPICAL OCULAR THERAPEUTIC DRUGS**NSAIDs**

- used for less serious chronic inflammatory conditions
- e.g. ketorolac (Acular®), diclofenac (Voltaren®), nepafenac (Nevanac®) drops

Anti-Histamines

- used to relieve red and itchy eye, often in combination with decongestants
- sodium cromoglycate – stabilizes membranes

Decongestants

- weak adrenergic stimulating drugs (vasoconstrictor)
- e.g. naphazoline, phenylephrine (Isopto Frin®)
- rebound vasodilation with overuse; rarely can precipitate angle closure glaucoma

Antibiotics

- indications: bacterial conjunctivitis, keratitis, or blepharitis
- commonly as topical drops or ointments, may give systemically
- e.g. sulfonamide (sodium sulfacetamide, sulfisoxazole), gentamicin (Garamycin®), erythromycin, tetracycline, bacitracin, polymyxin B, fluoroquinolones (Ciloxan®, Ocuflox®, Vigamox®, Zymar®)

Corticosteroids

- e.g. fluorometholone (FML®), betamethasone, dexamethasone (Maxidex®), prednisolone (Predsol® 0.5%, Pred Forte® 1%), rimexolone (Vexol®)
- primary care physicians should avoid prescribing topical corticosteroids due to risk of glaucoma, cataracts, and reactivation of HSV keratitis
- complications
 - potentiates herpes simplex keratitis and fungal keratitis as well as masks symptoms
 - increased IOP, more rapidly in steroid responders (within weeks)
 - posterior subcapsular cataract (within months)

References

Complications: Your eyes & diabetic retinopathy. Canadian Diabetes Association Nov 2003.

Diabetic Retinopathy. Diabetes Care 1998; 21(1):143-156.

Diabetes in Ontario: an ICES Practice Atlas. ICES June 2003.

Books

Bradford C. Basic Ophthalmology for Medical Students and Primary Care Residents. 7th ed. San Francisco: American Academy of Ophthalmology, 1999.

Wilson FM. Practical Ophthalmology: A Manual for Beginning Residents. 4th ed. American Academy of Ophthalmology, 2005.

Friedman N, Pineda R, Kaiser P. The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology. Toronto: W.B. Saunders Company, 1998.

Kanski JJ. Clinical Ophthalmology: A Systematic Approach. 6th ed. Oxford: Butterworth-Heinemann, 2007.

Stein R, Stein H. Management of Ocular Emergencies. 4th ed. Montreal: Mediconcept, 2006.

Guidelines

Hux J, et al. Diabetes in Ontario: an ICES Practice Atlas. Toronto: Institute for Clinical Evaluative Sciences, 2003.

The committee for the classification of retinopathy of prematurity. An international classification of retinopathy of prematurity. Arch Ophthalmology. 1984; 102: 1130-34.

Images

Red Atlas. www.redatlas.org

Atlas of Ophthalmology www.atlasophthalmology.com/atlas/frontpage.jsf

Lectures/Cases

University of Michigan Kellogg Eye Centre www.kellogg.umich.edu/theeyeshaveit/index.html

Frederick Cheng, Chris Farlinger and Caroline Scott, chapter editors

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Basic Anatomy Review

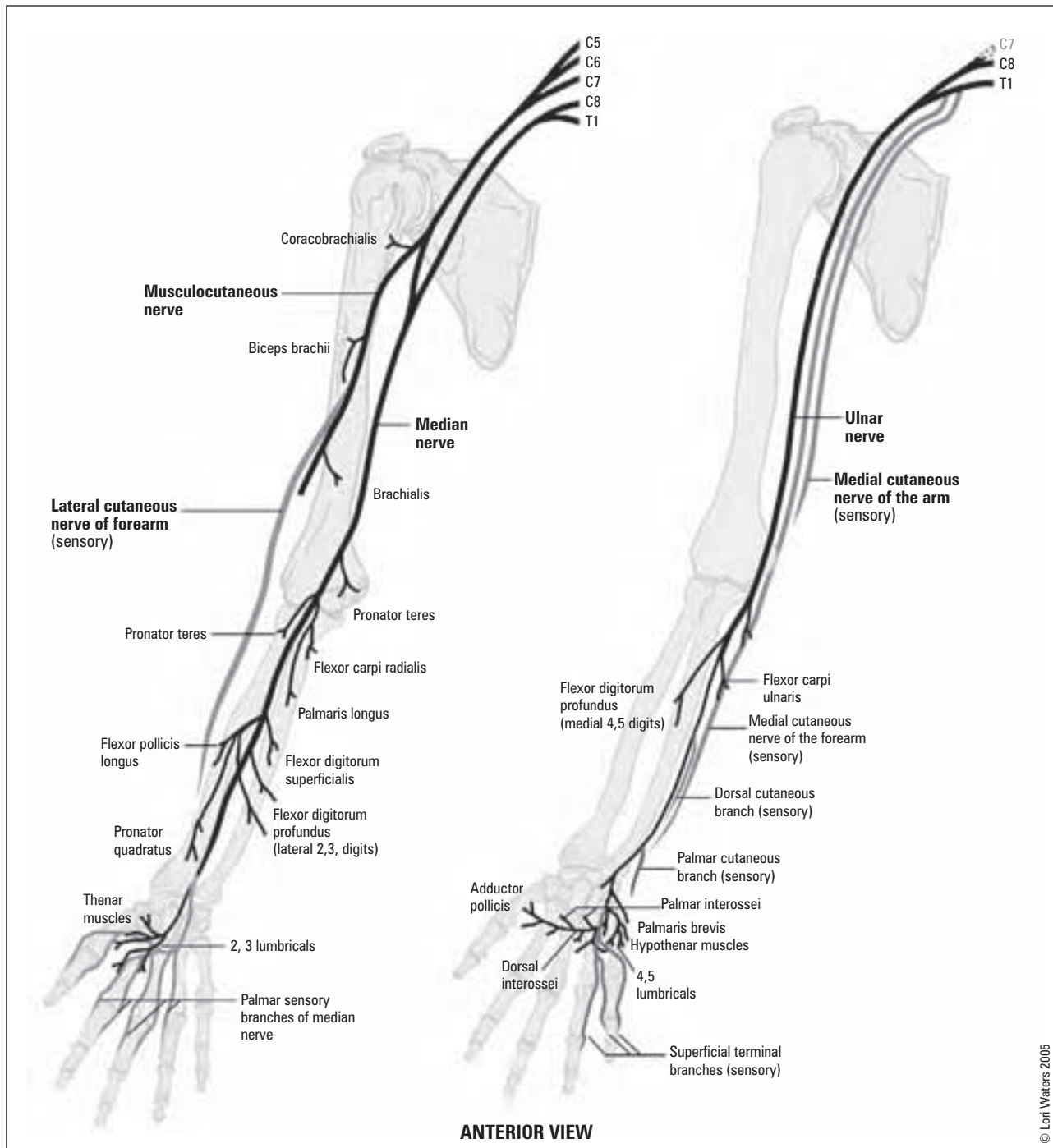
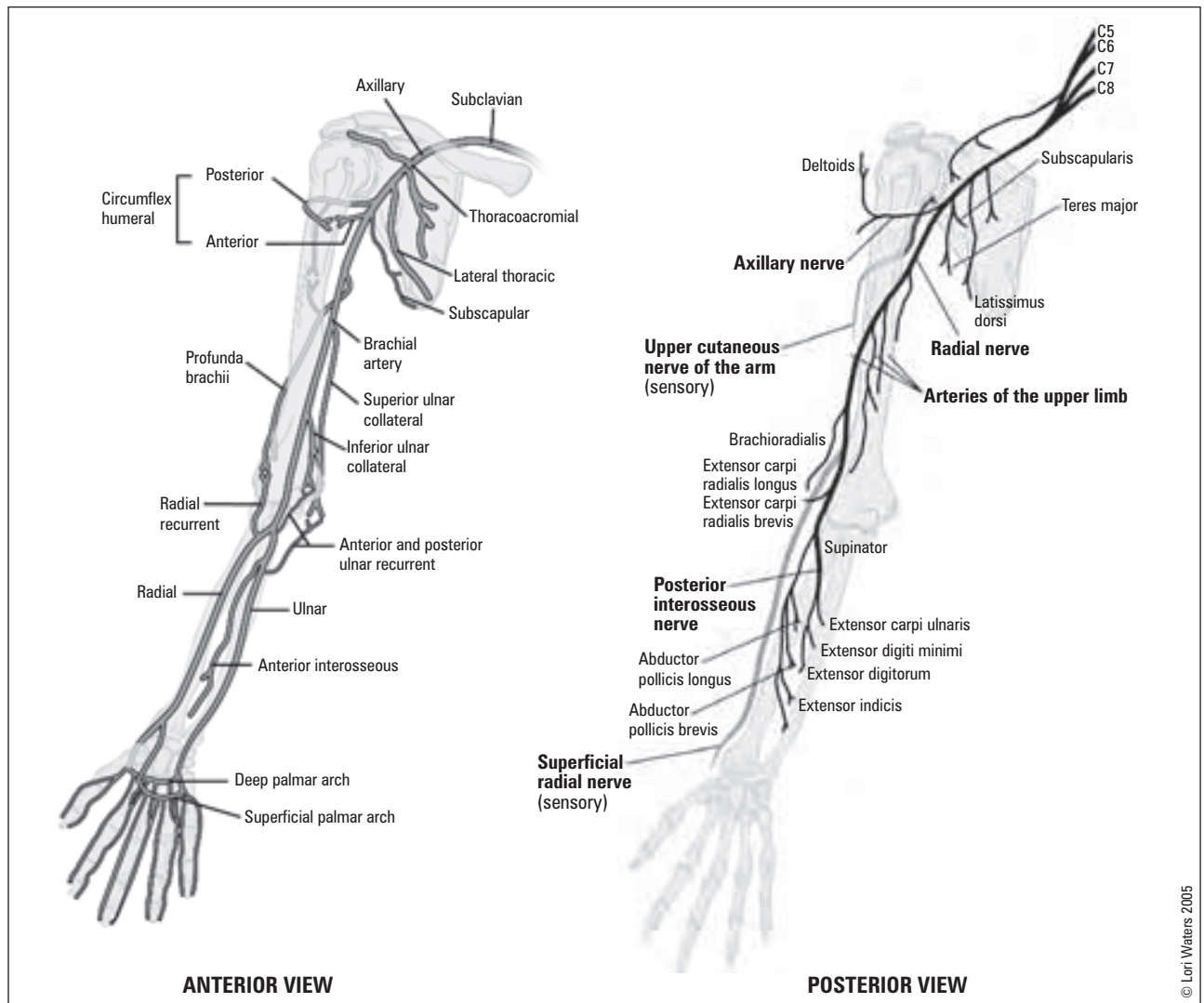


Figure 1. Median, Musculocutaneous and Ulnar Nerves: Innervation of Upper Limb Muscles



**Figure 2. (Left) Blood Supply to the Upper Limb
(Right) Axillary and Radial Nerves: Innervation of the Upper Limb**

Table 1. Sensory and Motor Innervation of the Nerves in the Upper and Lower Extremities

Nerve	Motor	Sensory
Axillary	Deltoid/Teres Minor	Lateral Upper Arm (Sergeant's Patch)
Musculocutaneous	Biceps/Brachialis	Lateral Forearm
Radial	Triceps Wrist/Thumb/Finger Extensors	Lateral Dorsum of the Hand Medial Upper Forearm
Median	Wrist Flexors and Abductors Flexion of the 1 st - 3 rd Digits	Volar Thumb to Radial ½ of Ring Finger
Ulnar	Wrist Flexors and Adductors Flexion of the 4 th - 5 th Digits	Medial Forearm Medial Dorsum and Volar of Hand (Ulnar ½ of Ring and 5 th Digit)
Tibial	Ankle Plantar Flexion Knee Flexion Great Toe Flexion	Sole of Foot
Superficial Peroneal	Ankle Eversion	Dorsum of Foot
Deep Peroneal	Ankle Dorsiflexion and Inversion Great Toe Extension	1 st Web Space
Sural		Lateral Foot
Saphenous		Anteromedial Ankle



Quick Nerve Exam
 "Thumbs Up": PIN (Radial Nerve)
 "OK Sign": AIN (Median Nerve)
 "Spread Fingers": Ulnar Nerve

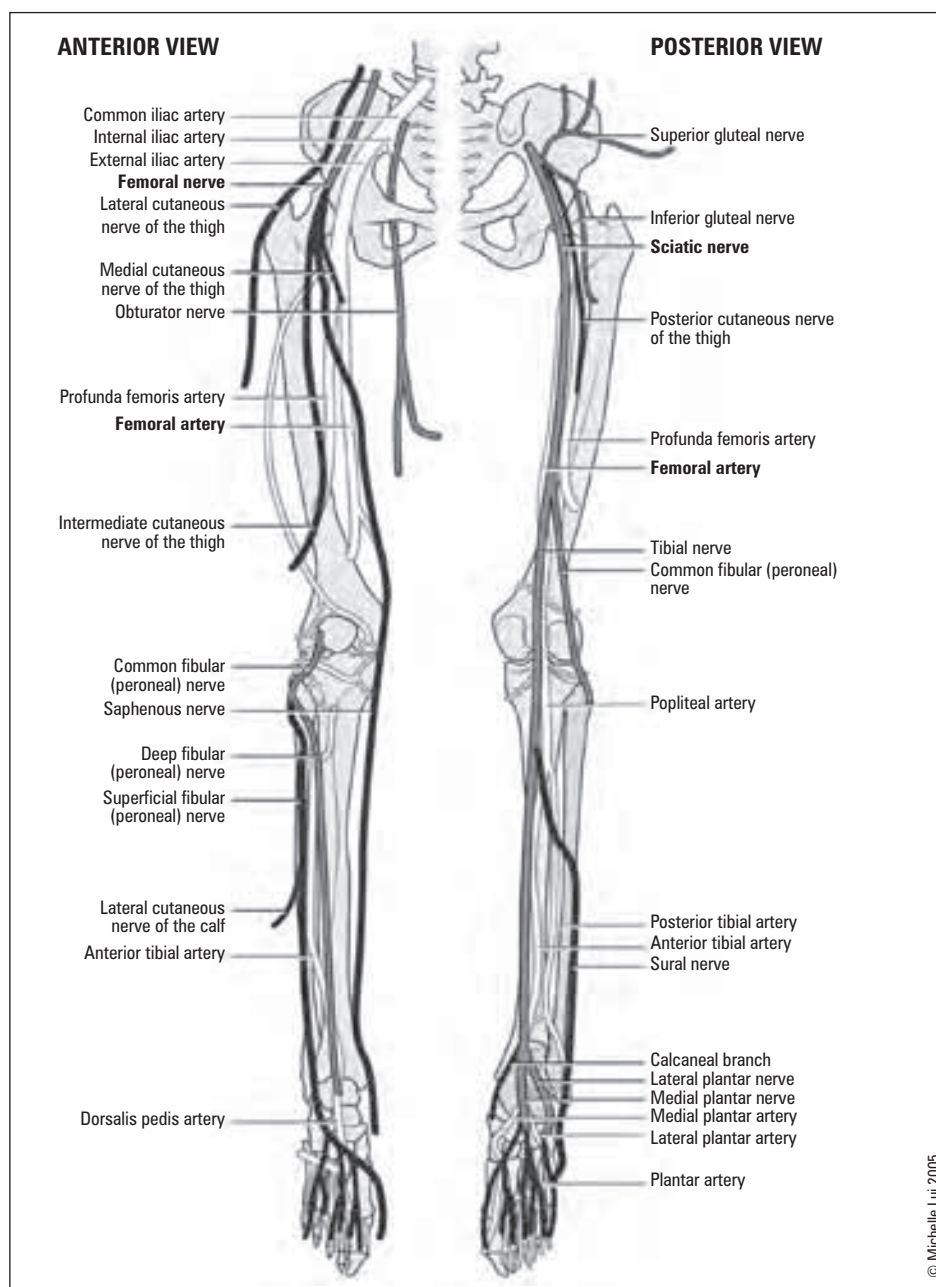


Figure 3. Nerves and Arteries of Lower Limbs

Differential Diagnosis of Joint Pain

Extrinsic

- neurologic (nerve root compression, herpes zoster, etc.)
- generalized (fibromyalgia, polymyalgia rheumatica, sickle cell (ischemic), dermatomyositis)
- referred pain
- pain originating from surrounding organs

Intrinsic

- articular
 - arthritis (degenerative, rheumatoid, crystal-induced, septic, avascular necrosis)
 - neoplastic
 - traumatic (fracture, soft tissue damage, neuropathic arthropathy)
- non-articular
 - bursa, tendons, ligaments, muscle (bursitis, tendonitis, myositis)

Fractures – General Principles



Fracture Description

1. Integrity of Skin/Soft Tissue

- closed: skin/soft tissue over and near fracture is intact
- open: skin/soft tissue over and near fracture is lacerated or abraded, fracture exposed to outside environment, continuous bleeding from puncture site or fat droplets in blood suggest communication with fracture

2. Location (Figure 4)

- epiphyseal: end of bone, forming part of the adjacent joint
- metaphyseal: the flared portion of the bone at the ends of the shaft
- diaphyseal: the shaft of a long bone (proximal, middle, distal)
- physis: growth plate

3. Orientation/Fracture Pattern (Figure 5)

- transverse: perpendicular fracture line, direct force, high energy
- oblique: angular fracture line, angular or rotational force
- butterfly: slight comminution at the fracture site which looks like a butterfly
- segmental: a separate segment of bone bordered by fracture lines, high energy
- spiral: complex, multi-planar fracture line, rotational force, low energy
- comminuted/multi-fragmentary: more than 2 fracture fragments
- intra-articular: fracture line crosses articular cartilage and enters joint
- compression/impacted: impaction of bone, e.g. vertebrae, proximal tibia
- torus: a buckle fracture of one cortex, often in children (Figure 49)
- green-stick: an incomplete fracture of one cortex, often in children (Figure 49)
- pathologic: fracture through bone weakened by disease/tumour

4. Displacement (Figure 5)

- nondisplaced: fracture fragments are in anatomic alignment
- displaced: fracture fragments are not in anatomic alignment
- distracted: fracture fragments are separated by a gap
- angulated: direction of fracture apex, e.g. varus/valgus
- translated: percentage of overlapping bone at fracture site
- rotated: fracture fragment rotated about long axis of bone

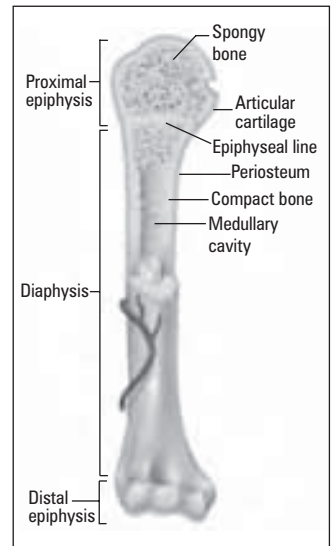


Figure 4. Schematic Diagram of the Long Bone



X-Ray Rule of 2's

- 2 sides = bilateral
- 2 views = AP + lateral
- 2 joints = joint above + below
- 2 times = before + after reduction



Varus/Valgus Displacement

Varus = Apex away from midline

Valgus = Apex toward midline

NOTE: displacement refers to direction of distal fragment.

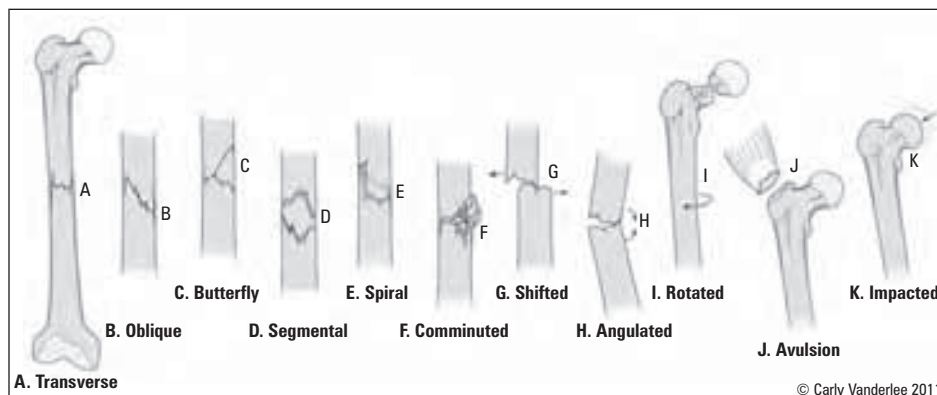


Figure 5. Fracture Types

Management of Fractures

- ABCs, primary survey and secondary survey (ATLS protocol)
 - rule out other fractures/injuries
 - rule out open fracture
- AMPLE history – Allergies, Medications, Past medical history, Last meal, Events surrounding injury
 - consider pathologic fracture with history of only minor trauma
- additional history/physical:
 - baseline functional status – handedness (upper extremity) vs. ambulatory ability (lower extremity – note distances, stairs, and use of assistive devices such as canes, walkers, wheelchairs, etc.)



Indications for Open Reduction

NO CAST

- N** – non-union
- O** – open fracture
- C** – neurovascular compromise
- A** – intra-articular fracture
- S** – Salter-Harris 3,4,5
- T** – polytrauma

**Reasons For Splinting**

- Reduces pain
- Reduces further damage to vessels, nerves and skin
- Reduces risk of inadvertently converting closed to open fracture
- Facilitates patient transport



Figure 6. Heterotopic Ossification of Femoral Diaphysis after Femur Fracture and Intramedullary Nailing

**Heterotopic Ossification**

The formation of bone in abnormal locations (e.g. in muscle), secondary to pathology.

**Avascular Necrosis**

Ischemia to bone due to disrupted blood supply; commonly in bones covered by cartilage.

**Fracture Blister**

Formation of vesicles or bullae that occur on edematous skin overlying a fractured bone.

**CRPS/Reflex Sympathetic Dystrophy**

An exaggerated response to an insult in the extremities; characterized by intense pain, temperature asymmetry, edema and motor/sensory changes.

- occupation and smoking status
- mechanism of injury
- past medical history (note any contraindications to surgery or general anesthetic)
- neurovascular status
- analgesia
- imaging
- splint extremity
- 1. obtain the reduction (refer to Table 22 for appropriate IV sedation)
 - closed reduction
 - ♦ apply traction in the long axis of the limb
 - ♦ reverse the mechanism that produced the fracture
 - ♦ reduce with IV sedation and muscle relaxation (fluoroscopy can be used if available)
 - indications for open reduction – NO CAST (see sidebar, OR5)
 - other indications include
 - ♦ failed closed reduction
 - ♦ cannot cast or apply traction due to site (e.g. hip fracture)
 - ♦ pathologic fractures
 - ♦ potential for improved function with open reduction and internal fixation (ORIF)
 - potential complications of open reductions
 - ♦ infection
 - ♦ mal-union
 - ♦ non-union
 - ♦ implant failure
 - ♦ new fracture
 - re-check neurovascular status after reduction and obtain post-reduction x-ray
- 2. maintain the reduction
 - external stabilization – splints, casts, traction, external fixator
 - internal stabilization – percutaneous pinning, extramedullary fixation (screws, plates, wires), intramedullary fixation (rods)
 - follow-up – evaluate bone healing
- 3. rehabilitate to regain function and avoid joint stiffness

Fracture Healing

Normal Healing

Weeks 0-3	Hematoma, macrophages surround fracture site
Weeks 3-6	Osteoclasts remove sharp edges, callus forms within hematoma
Weeks 6-12	Bone forms within the callus, bridging fragments
Months 6-12	Cortical gap is bridged by bone
Years 1-2	Normal architecture is achieved through remodelling

Figure 7. Stages of Bone Healing

Evaluation of Healing: Tests of Union

- clinical: no longer tender to palpation or stressing on physical exam
- x-ray: trabeculae cross fracture site, visible callus bridging site on at least 3 of 4 cortices

General Fracture Complications

Table 2. General Fracture Complications

	Early	Late
Local	Compartment syndrome Neurological injury Vascular injury Infection Implant failure Fracture blisters	Mal/non-union Avascular necrosis (AVN) Osteomyelitis Heterotopic ossification (HO) Post-traumatic arthritis/Joint stiffness Chronic regional pain syndrome type 1 (CRPS)/Reflex sympathetic dystrophy (RSD)
Systemic	Sepsis Deep vein thrombosis (DVT) Pulmonary embolus (PE) Acute respiratory distress syndrome (ARDS) Hemorrhagic shock	

Orthopaedic Emergencies

Trauma Patient Work-Up

Etiology

- high energy trauma e.g. motor vehicle accidents, fall from height
- may be associated with spinal injuries or life-threatening visceral injuries

Clinical Presentation

- local swelling, tenderness, deformity of the limbs and instability of the pelvis or spine
- decreased level of consciousness
- consider involvement of alcohol or other substances

Investigations

- trauma survey (see Emergency Medicine, Initial Patient Assessment/Management, ER2)
- x-rays: lat cervical spine, AP chest, abdo x-ray, AP pelvis, AP and lateral of all long bones suspected to be injured
- other views of pelvis: AP, inlet and outlet; Judet view for acetabular fracture (see Table 15 for classification of pelvic fractures)

Treatment

- ABCDEs and initiate resuscitation to life threatening injuries
- assess genitourinary injury (rectal exam/vaginal exam mandatory)
- external or internal fixation of all fractures
- DVT prophylaxis

Complications

- **hemorrhage – life threatening** (may produce signs and symptoms of hypovolemic shock)
- acute respiratory distress syndrome (ARDS)
- fat embolism syndrome
- venous thrombosis – DVT and PE
- bladder/bowel injury
- neurological damage
- possible obstetrical difficulties in future
- persistent sacro-iliac joint pain
- persistent pain/stiffness/limp/weakness in affected extremities
- post-traumatic arthritis of joints with intra-articular fractures
- sepsis if missed open fracture

Open Fractures

Definition

- fractured bone in communication with the external environment

Emergency Measures

- removal of obvious foreign material
- irrigate with normal saline
- cover wound with sterile dressings
- IV antibiotics (see Table 3)
- tetanus status \pm booster
- splint fracture
- NPO and prepare for OR (bloodwork, consent, ECG, CXR)
 - operative irrigation and debridement within 6-8 hours to decrease risk of infection
 - traumatic wound often left open to drain but vac dressing may be used
 - re-examine with repeat I&D in 48 hrs



Orthopaedic Emergencies

VON CHOP

Vascular compromise
Open fracture
Neurological compromise/Cauda equina syndrome
Compartment syndrome
Hip dislocation
Osteomyelitis/Septic arthritis
Unstable Pelvic fracture



Buck's Traction

A system of weights, pulleys and ropes that are attached to the end of a patient's bed exerting a longitudinal force on the distal end of a fracture, improving its alignment.



33% of patients with open fractures have multiple injuries.

Table 3. Gustilo Classification of Open Fractures

Gustilo Grade	Length of Open Wound	Description	Antibiotic Regimen
I	<1 cm	Minimal contamination and soft tissue injury Simple or minimally comminuted fracture	First generation cephalosporin (cefazolin) for 3 days
II	1-10 cm	Moderate contamination Soft tissue injury	First generation cephalosporin (cefazolin) for 3 days plus Gram-negative coverage (gentamicin) for at least 3 days
III*	>10 cm	IIIA: Extensive soft tissue injury with adequate ability of soft tissue to cover wound IIIB: Extensive soft tissue injury with periosteal stripping and bone exposure; inadequate soft tissue to cover wound IIIC: Vascular injury/compromise	First generation cephalosporin (cefazolin) plus Gram-negative coverage (gentamicin) for at least 3 days For soil contamination, penicillin is added for clostridial coverage

*Any high injury, comminuted fracture, shot gun, farmyard/soil/water contamination, exposure to oral flora, or fracture more than 8 hours old is immediately classified as Grade III

Septic Joint

Etiology

- most commonly caused by *Staphylococcus aureus* in adults
- consider coagulase-negative staph in patients with prior joint replacement
- consider *Neisseria gonorrhoeae* in sexually active adults
- most common route of infection is hematogenous

Clinical Presentation

- inability/refusal to bear weight, localized joint pain, erythema, warmth, swelling with pain on active and passive ROM, \pm fever

Investigations

- x-ray (to r/o fracture, tumour, metabolic bone disease), ESR, CRP, WBC, blood cultures
- joint aspirate (WBC >80,000 with >90% neutrophils, protein level >4.4 mg/dL, joint << blood glucose level, no crystals, positive Gram stain results)
- rule out heart murmurs

Treatment

- IV antibiotics, empiric therapy (based on age and risk factors), adjust pending joint aspirate C&S
- for small joints: needle aspiration, serial if necessary until sterile
- for major joints such as knee, hip, or shoulder: urgent decompression and surgical drainage



Plain Film Findings in a Septic Joint

- Early (0-3 days) – usually normal.
May show soft-tissue swelling or joint space widening from localized edema
- Late (4-6 days) – joint space narrowing and destruction of cartilage



Serial C-reactive protein (CRP) can be used to monitor response to therapy.



Osteomyelitis

Etiology

- most common organism is *Staphylococcus aureus*
- consider *Salmonella typhi* in patients with sickle cell disease
- neonates and immunocompromised patients are susceptible to Gram-negative organisms
- hematogenous (bacteremia) or exogenous (open fractures, surgery, local infected tissue) spread

Clinical Presentation

- localized extremity pain \pm fever or swelling 1 to 2 weeks after respiratory infection or infection at another non-bony site

Investigations

- blood culture, aspirate cultures, ESR, CRP, CBC (leukocytosis)
- x-ray, bone scan (increased uptake within 24-48 hours after onset in majority of patients), MRI most sensitive/specific

Treatment

- IV antibiotics, empiric therapy, adjust pending blood and aspirate cultures
- surgical debridement and drainage \pm local antibiotics (e.g. antibiotic beads) if MRI suggests an abscess or if patient does not improve after 36 hours on IV antibiotics
- serial I&D (if required), IV antibiotics eventually changed to PO, splint limb for several weeks followed by protective weight-bearing of the limb



Plain Film Findings of Osteomyelitis

1. Soft tissue swelling
2. Lytic bone destruction*
3. Periosteal reaction (formation of new bone, especially in response to #)*

*Generally not seen on plain films until 10-12 days after onset of infection.



Acute osteomyelitis is a medical emergency which requires an early diagnosis and appropriate antimicrobial and surgical treatment.

Compartment Syndrome

Definition

- increased interstitial pressure in an anatomical “compartment” (forearm, calf) where muscle and tissue are bounded by fascia and bone (fibro-osseous compartment) with little room for expansion
- interstitial pressure exceeds capillary perfusion pressure leading to muscle necrosis (in 4-6 hrs) and eventually nerve necrosis

Etiology

- intracompartmental: fracture (particularly tibial shaft fractures, pediatric supracondylar fractures, and forearm fractures), crush injury, revascularization
- extracompartmental: constrictive dressing (circumferential cast), circumferential burn

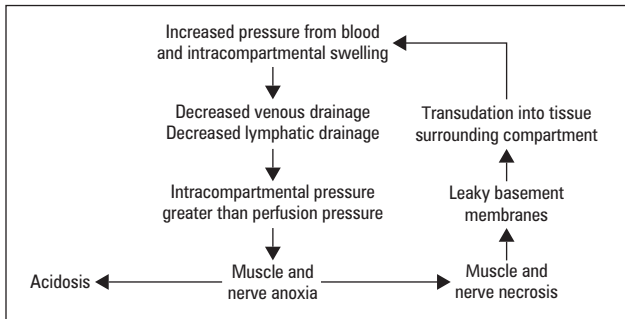


Figure 8. Pathogenesis of Compartment Syndrome

Physical Examination

- pain with passive stretch
- 5 P's: late sign (see sidebar)

Clinical Features

- pain with active contraction of compartment
- pain with passive stretch
- swollen, tense compartment
- suspicious history

Investigations

- usually not necessary as compartment syndrome is a clinical diagnosis
- in children or unconscious patients where clinical exam is unreliable, compartment pressure monitoring with catheter AFTER clinical diagnosis is made (normal = 0 mmHg; elevated ≥ 30 mmHg or ≤ 30 mmHg of diastolic BP)

Treatment

- non-operative
 - remove constrictive dressings (casts, splints), elevate limb at the level of the heart
- operative
 - urgent fasciotomy
 - 48-72 hours post-op: wound closure \pm necrotic tissue debridement

Specific Complications

- rhabdomyolysis, renal failure secondary to myoglobinuria
- Volkmann's ischemic contracture: ischemic necrosis of muscle, followed by secondary fibrosis and finally calcification; especially following supracondylar fracture of humerus

Cauda Equina Syndrome

- see Neurosurgery, NS27



5 P's of Compartment Syndrome

- Pain**
 - Out of proportion for injury
 - Not relieved by analgesics
 - Increased with passive stretch of compartment muscles (most specific)
- Pallor**: late finding
- Paresthesia**
- Paralysis**: late finding
- Pulselessness**: late finding



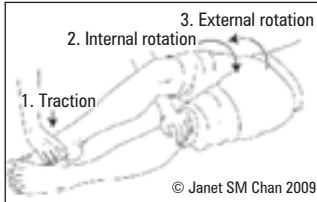
Most important sign is increased pain with passive stretch. Most important symptom is pain out of proportion to injury.



Cauda equina syndrome is a surgical emergency.



Up to 50% of patients with hip dislocations suffer fractures elsewhere at the time of injury.



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Figure 9. Rochester Method



Rochester Method to Reduce Dislocations

- Patient lying supine with hip and knee flexed on injured side
- Surgeon stands on patient's injured side
- Surgeon passes one arm under patient's flexed knee, reaching to place that hand on patient's other knee (thus supporting patient's injured leg)
- With other hand, surgeon grasps patient's ankle on injured side, applying traction
- Reduction via traction, int. rotation, then ext. rotation once femoral head clears acetabular rim

Hip Dislocation

- full trauma survey (see *Emergency Medicine, Initial Patient Assessment/Management*, ER2)
- examine for neurovascular injury PRIOR to open or closed reduction
- reduce hip dislocations ASAP (ideally within 6 hours) to decrease risk of AVN of the femoral head
- hip precautions (no extreme hip flexion, adduction, internal or external rotation) for 6 weeks post-reduction
- also see *Hip Dislocation after THA*, OR28

ANTERIOR HIP DISLOCATION

- mechanism: posteriorly directed blow to knee with hip widely abducted
- clinical features: shortened, abducted, externally rotated limb
- treatment
 - closed reduction under conscious sedation/GA
 - post-reduction CT to assess joint congruity

POSTERIOR HIP DISLOCATION

- most frequent type of hip dislocation
- mechanism: severe force to knee with hip flexed and adducted
 - e.g. knee into dashboard in motor vehicle accident (MVA)
- clinical features: shortened, adducted and internally rotated limb
- treatment
 - closed reduction under conscious sedation/GA only if associated femoral neck fracture
 - ORIF if unstable, intra-articular fragments or posterior wall fracture
 - post-reduction CT to assess joint congruity and fractures
 - if reduction is unstable, put in traction x 4-6 weeks

CENTRAL HIP DISLOCATION (rare)

- traumatic injury where femoral head is pushed through acetabulum toward pelvic cavity

COMPLICATIONS FOR ALL HIP DISLOCATIONS

- post-traumatic arthritis
- AVN
- fracture of femoral head, neck, or shaft
- sciatic nerve palsy in 25% (10% permanent)
- heterotopic ossification (HO)
- thromboembolism – DVT/PE

Pelvis

Pelvic Fracture

Mechanism

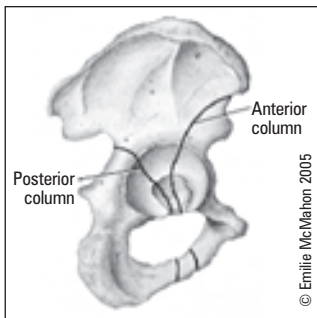
- young: high energy trauma, either direct or by force transmitted longitudinally through the femur
- elderly: fall from standing height, low energy trauma

Clinical Features

- local swelling, tenderness
- deformity of lower extremity
- pelvic instability

Investigations

- x-ray: AP pelvis, inlet and outlet for pelvic fracture
 - Judet films (obturator and iliac oblique) for acetabular fracture
 - 6 cardinal radiographic lines of the acetabulum: ilioischial line, iliopectineal line, tear drop, roof, posterior rim, anterior rim
- CT scan useful for evaluating posterior pelvic injury and acetabular fracture



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Figure 10. Pelvic Columns

Classification

Table 4. Tile Classification of Pelvic Fractures (see Figure 11)

Type	Stability	Description
A	Rotationally stable Vertically stable	A1: fracture not involving pelvic ring A2: minimally displaced fracture of pelvic ring (e.g. ramus fracture)
B	Rotationally unstable Vertically stable	B1: open book B2: lateral compression – ipsilateral B3: lateral compression – contralateral
C	Rotationally unstable Vertically unstable	C1: unilateral C2: bilateral C3: associated acetabular fracture

Treatment

- ABCs
- assess genitourinary injury (rectal exam, vaginal exam, hematuria, blood at urethral meatus)
 - if involved, the fracture is considered an open fracture
- stable fractures – nonoperative treatment, protected weight bearing
- indications for operative treatment
 - unstable pelvic ring injury
 - disruption of anterior and posterior SI ligament
 - symphysis diastasis >2.5 cm
 - vertical instability of the posterior pelvis

Specific Complications (see General Fracture Complications, OR6)

- **hemorrhage (life-threatening)** – 1500-3000 ml blood loss
- injury to rectum or urogenital structures
- obstetrical difficulties
- persistent sacroiliac (SI) joint pain
- post-traumatic arthritis of the hip with acetabular fractures
- high risk of DVT/PE

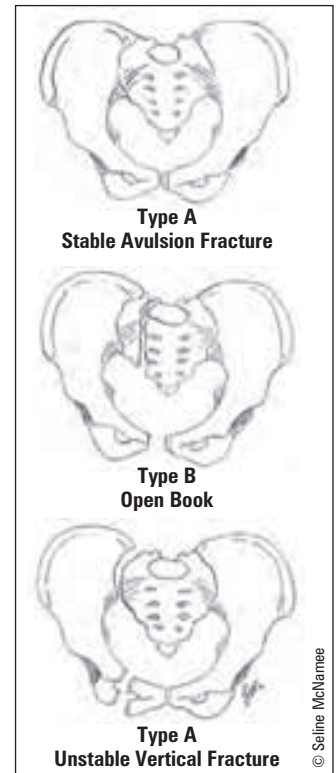


Figure 11. Illustration of the Tile Classification of Pelvic Fractures

Shoulder

Shoulder Dislocation

- the glenohumeral joint is the most commonly dislocated joint in the body since stability is sacrificed for motion

Prognosis

- recurrence rate depends on age of 1st dislocation: <20 yrs = 65-95%; 20-40 yrs = 60-70%; >40 yrs = 2-4%

Specific Complications

- tuberosity fracture, glenoid rim fracture (Bankart lesion), humeral head impaction (Hill-Sachs lesion)
- rotator cuff or capsular tear, shoulder stiffness
- injury to axillary nerve/artery, brachial plexus
- recurrent/unreduced dislocation (most common complication)

ANTERIOR SHOULDER DISLOCATION (>90%)

Mechanism

- abducted and externally rotated arm or blow to posterior shoulder

Clinical Features

- pain
- arm held in slight abduction, external rotation; internal rotation is blocked
- “squared off” shoulder
- +ve apprehension test: apprehension with shoulder abduction and external rotation to 90° since humeral head is pushed anteriorly and recreates feeling of anterior dislocation
- +ve relocation test: a posteriorly directed force applied during the apprehension test relieves apprehension since anterior subluxation is prevented



There are 4 Joints in the Shoulder: glenohumeral, acromioclavicular (AC), sternoclavicular (SC), scapulothoracic.



Factors Causing Shoulder Instability

- Shallow glenoid
- Loose capsule
- Ligamentous laxity

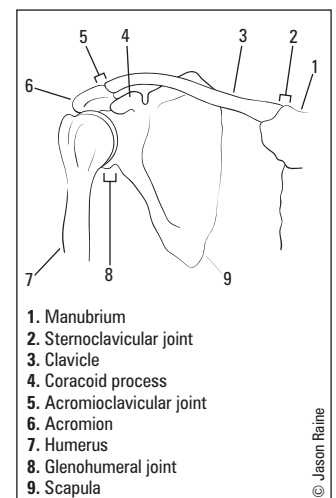


Figure 12. Shoulder Joints



Anterior apprehension sign



Sulcus sign



Posterior apprehension sign

Figure 13. Apprehension Tests



Figure 14. Traction-Countertraction

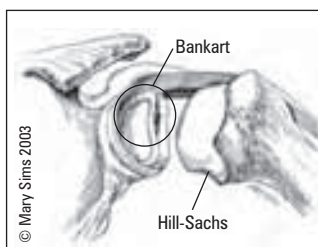


Figure 15. Anterior Dislocation Causing Hill-Sachs and Bankart Lesions

- +ve sulcus sign: presence of subacromial indentation with distal traction on humerus indicates inferior shoulder instability
- neurovascular exam including:
 - axillary nerve (sensory patch over deltoid and deltoid contraction)
 - musculocutaneous nerve (sensory patch on lateral forearm and biceps contraction)

Table 5. An EBM Perspective on Tests of Anterior Shoulder Instability

	Apprehension	Relocation	Surprise
Sensitivity	52.78%	45.83%	63.89%
Specificity	98.91%	54.35%	98.91%
PPV	97.73%	43.86%	98.22%
NPV	72.82%	56.26%	77.86%

An Evaluation of the Apprehension, Relocation, and Surprise Tests for Anterior Shoulder Instability. *The American Journal of Sports Medicine* 32:301-307 (2004).

Investigations

- x-rays: AP, trans-scapular, axillary

X-Ray Findings

- dislocation
 - axillary view: humeral head is anterior
 - trans-scapular view: humeral head is anterior to the centre of the "Mercedes-Benz sign"
- \pm Hill-Sachs lesion: divot in posterior humeral head due to forceful impaction of an anteriorly dislocated humeral head against the glenoid rim (Figure 15)
- \pm bony Bankart lesion: avulsion of the anterior glenoid labrum (with attached bone fragments) from the glenoid rim

Treatment

- closed reduction with IV sedation and muscle relaxation
- 2 methods
 - traction-countertraction: assistant stabilizes torso with a folded sheet wrapped across the chest while the MD applies gentle steady traction (see Figure 14)
 - Stimson: while patient lies prone with arm hanging over table edge, hang a 5 lb weight on wrist for 15-20 min
- obtain post-reduction x-rays
- check post-reduction neurovascular status (NVS)
- sling x 3 weeks, followed by shoulder rehabilitation

POSTERIOR SHOULDER DISLOCATION (5%)

- up to 60-80% are missed on initial presentation due to poor physical exam and radiographs

Mechanism

- adducted, internally rotated, flexed arm
- fall on an outstretched hand (FOOSH)
- 3 E's (epileptic seizure, EtOH, electrocution)
- blow to anterior shoulder

Clinical Features

- arm is held in adduction and internal rotation; external rotation is blocked
- anterior shoulder flattening, prominent coracoid, palpable mass posterior to shoulder
- posterior apprehension ("jerk") test: with patient supine, flex elbow 90° and adduct, internally rotate the arm while applying a posterior force to the shoulder; patient will "jerk" back with the sensation of subluxation

Investigation

- x-rays: AP, trans-scapular, axillary

X-Ray Findings

- dislocation
 - AP view: partial vacancy of glenoid fossa (vacant glenoid sign) and >6 mm space between anterior glenoid rim and humeral head (positive rim sign), humeral head may resemble a lightbulb due to internal rotation (lightbulb sign)
 - axillary view: humeral head is posterior
 - trans-scapular view: humeral head is posterior to centre of "Mercedes-Benz sign"
- reverse Hill-Sachs lesion (75% of cases): divot in anterior humeral head
- reverse bony Bankart lesion: avulsion of the posterior glenoid labrum from the bony glenoid rim

Treatment

- closed reduction: inferior traction on a flexed elbow with pressure on the back of the humeral head
- obtain post-reduction x-rays
- check post-reduction neurovascular status
- sling x 3 weeks, followed by shoulder rehabilitation

Rotator Cuff Disease

- rotator cuff consists of 4 muscles that act to stabilize humeral head within the glenoid fossa

Table 6. Rotator Cuff Muscles

Muscle	Muscle Attachments	Nerve Supply	Muscle Function
Supraspinatus	Scapula → greater tuberosity of humerus	Suprascapular nerve	Abduction
Infraspinatus	Scapula → greater tuberosity of humerus	Suprascapular nerve	External rotation
Teres Minor	Scapula → greater tuberosity of humerus	Axillary nerve	External rotation
Subscapularis	Scapula → lesser tuberosity of humerus	Subscapular nerve	Internal rotation and adduction

SPECTRUM OF DISEASE: IMPINGEMENT, TENDONITIS, MICRO OR MACRO TEARS

Etiology

- compression of rotator cuff tendons (primarily supraspinatus) and subacromial bursa between the head of the humerus and the acromion; leads to bursitis, tendonitis and, if left untreated, can lead to rotator cuff thinning and tear
- anything that leads to a narrow subacromial space
 1. glenohumeral muscle weakness leading to abnormal motion of humeral head
 2. scapular muscle weakness leading to abnormal motion of acromion
 3. acromial abnormalities such as congenital narrow space or osteophyte formation

Clinical Features

- night pain and difficulty sleeping on affected side
- pain worse with active motion
- weakness and loss of range of motion (e.g. trouble with overhead activities)
- tenderness to palpation over greater tuberosity

Table 7. Rotator Cuff Special Tests

Test	Examination	Positive Test
Jobe's Test	Supraspinatus – place the shoulder in 90 degrees of abduction and 30 degrees of forward flexion and internally rotate the arm so that the thumb is pointing toward the floor (Figure 17)	Weakness with active resistance suggests a supraspinatus tear
Lift-off Test	Subscapularis – internally rotate arm so dorsal surface of hand rests on lower back. Patient instructed to actively lift hand away from back against examiner resistance (Figure 17)	Inability to actively lift hand away from back suggests a subscapularis tear
Posterior-cuff Test	Infraspinatus and Teres minor – arm positioned at patient's side in 90 degrees of flexion. Patient instructed to externally rotate arm against the resistance of the examiner (Figure 17)	Weakness with active resistance suggests posterior cuff tear
Neer's Test	Rotator Cuff Impingement – passive shoulder flexion (Figure 18)	Pain elicited between 130-170 degrees suggests impingement
Hawkins-Kennedy Test	Rotator Cuff Impingement – shoulder flexion to 90 degrees and passive internal rotation (Figure 19)	Pain with internal rotation suggests impingement
Painful Arc Test	Rotator Cuff Tendinopathy – patient instructed to actively abduct the shoulder	Pain with abduction greater than 90 degrees suggests tendinopathy



Rotator Cuff Muscles

SITS

Supraspinatus
Infraspinatus
Teres minor
Subscapularis

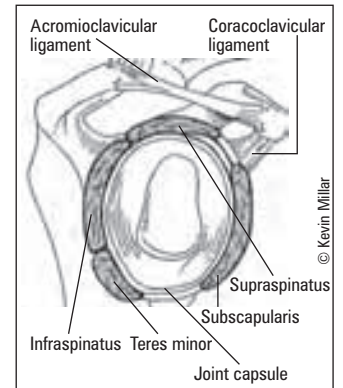


Figure 16. Muscles of the Rotator Cuff

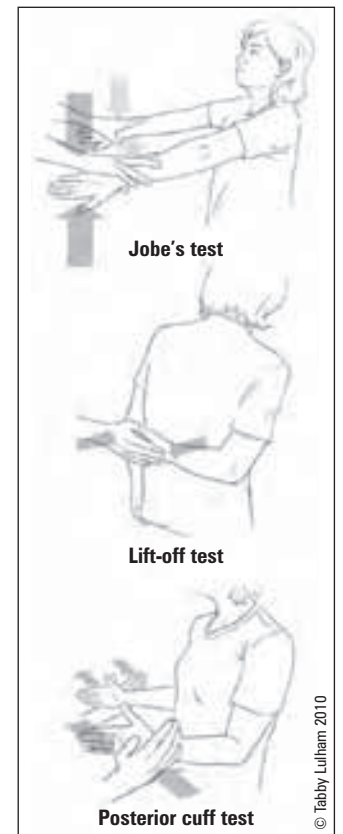


Figure 17. Rotator Cuff Tests – Jobe's, Lift-Off, Posterior Cuff



Figure 18. Neer's Test

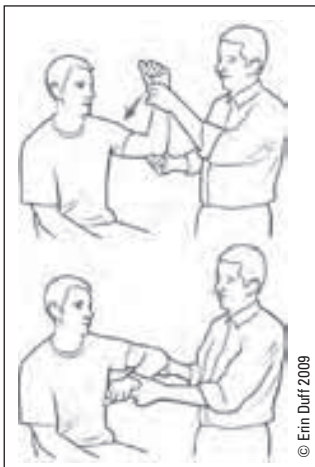


Figure 19. Hawkins-Kennedy Test



Pneumothorax or pulmonary contusion are potential complications of severe acromioclavicular joint dislocation



Associated Injuries with Clavicular Fractures

- Up to 9% of clavicular fractures are associated with other fractures (most commonly rib fractures)
- Majority of brachial plexus injuries are associated with proximal third fractures

Investigations

- x-rays: AP view may show high riding humerus relative to glenoid, evidence of chronic tendonitis
- MRI: coronal/sagittal oblique and axial orientations are useful for assessing full/partial tears and tendinopathy, ± arthrogram: geyser sign (injected dye leaks out of joint through rotator cuff tear)
- arthrogram: see full thickness tear, difficult to assess partial thickness tears

Treatment and Prognosis

- mild ("wear")
 - treatment is non-operative (physiotherapy, NSAIDs)
- moderate ("tear")
 - non-operative treatment ± steroid injection
- severe ("repair")
 - impingement that is refractory to 2-3 months physio and 1-2 injections
 - may require surgical repair, i.e. acromioplasty, rotator cuff repair

Acromioclavicular (AC) Joint Pathology

- 2 main ligaments attach clavicle to scapula: acromioclavicular (AC) and coracoclavicular (CC) ligaments

Mechanism

- fall onto shoulder with adducted arm (fall onto tip of shoulder)

Clinical Features

- palpate step deformity between distal clavicle and acromion (with dislocation)
- pain with adduction of shoulder and/or palpation over AC joint
- limited ROM

Investigations

- x-rays: AP, Zanca view (10-15° cephalic tilt), axillary ± stress views (10 lb weight in patient's hand)

Treatment

- non-operative (most-common): sling 1-3 weeks, ice, analgesia
- operative
 - indications: AC and CC ligaments are both torn and/or clavicle displaced posteriorly
 - procedure: excision of lateral clavicle with AC/CC ligament reconstruction

Clavicular Fracture

- incidence: proximal (5%), middle (80%), or distal (15%) third of clavicle
- common in children (unites rapidly without complications)

Mechanism

- fall on shoulder (87%), direct trauma to clavicle (7%), FOOSH (6%)

Clinical Features

- pain and tenting of skin
- arm is clasped to chest to splint shoulder and prevent movement

Treatment

- evaluate neurovascular status of entire upper limb
- proximal and middle third clavicular fractures
 - sling x 1-2 weeks
 - early ROM and strengthening once pain subsides
 - if ends overlap >2 cm, consider ORIF
- distal third clavicular fractures
 - undisplaced (with ligaments intact): sling x 1-2 weeks
 - displaced (CC ligament injury): ORIF

Specific Complications (see *General Fracture Complications*, OR6)

- cosmetic bump usually only complication
- shoulder stiffness, weakness with repetitive activity
- pneumothorax, injuries to brachial plexus and subclavian vessel (all very rare)

Frozen Shoulder (Adhesive Capsulitis)



Definition

- disorder characterized by progressive pain and stiffness of the shoulder usually resolving spontaneously after 18 months

Mechanism

- primary adhesive capsulitis
 - idiopathic, usually associated with diabetes mellitus
 - may resolve spontaneously in 9-18 months
- secondary adhesive capsulitis
 - due to prolonged immobilization
 - shoulder-hand syndrome – type of chronic regional pain syndrome (reflex sympathetic dystrophy) characterized by arm and shoulder pain, decreased motion and diffuse swelling
 - following myocardial infarction, stroke, shoulder trauma

Clinical Features

- gradual onset (weeks to months) of diffuse shoulder pain with:
 - decreased active and passive ROM
 - pain worse at night and often prevents sleeping on affected side
 - increased stiffness as pain subsides: continues for 6-12 months after pain has disappeared

Investigations

- x-rays may be normal, or may show demineralization from disease

Treatment

- active and passive ROM (physiotherapy)
- NSAIDs and steroid injections if limited by pain
- MUA (manipulation under anesthesia) and early physiotherapy
- arthroscopy for debridement/decompression



Conditions Associated with an Increased Incidence of Adhesive Capsulitis

- Prolonged immobilization (most significant)
- Female gender
- Age >49 years
- Diabetes mellitus (5x)
- Cervical disc disease
- Hyperthyroidism
- Stroke
- Myocardial infarction
- Trauma and surgery

Humerus

Proximal Humeral Fracture

Mechanism

- young: high energy trauma (MVA)
- older: FOOSH from standing height in osteoporotic individuals

Clinical Features

- pain, swelling, tenderness, painful ROM

Investigations

- test axillary nerve function (deltoid function and skin over deltoid)
- x-rays: AP, trans-scapular, axillary are essential
- CT scan: to evaluate for articular involvement and fracture displacement

Classification

- Neer classification is based on 4 fracture fragments: head, greater tuberosity, lesser tuberosity, shaft
 - nondisplaced: displacement <1 cm and/or angulation <45°
 - displaced: displacement >1 cm and/or angulation >45°
 - dislocated/subluxed: humeral head dislocated/subluxed from glenoid

Treatment

- non-operative
 - sling immobilization (nondisplaced): begin ROM in 7-10 days to prevent stiffness
 - closed reduction (minimally displaced)
- operative
 - ORIF (anatomic neck fractures, displaced, dislocated)
 - hemiarthroplasty may be necessary, especially in elderly

Specific Complications (see *General Fracture Complications*, OR6)

- AVN, axillary nerve palsy, malunion, post-traumatic arthritis



Anatomic neck fractures disrupt blood supply to the humeral head and avascular necrosis (AVN) of the humeral head may ensue.

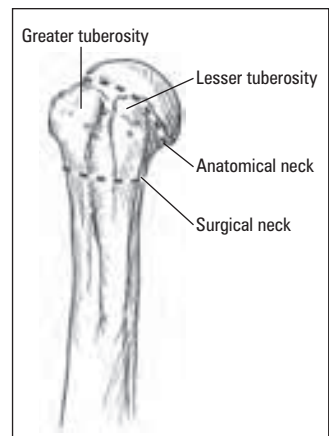


Figure 20. Fractures of the Proximal Humerus



Neer Classification

Based on 4 parts of humerus

- Greater Tuberosity
- Lesser Tuberosity
- Humeral Head
- Shaft

Two-part fracture: any of the 4 parts with 1 displaced

Three-part fracture: displaced fracture of surgical neck + displaced greater tuberosity or lesser tuberosity

Four-part fracture: displaced fracture of surgical neck + both tuberosities

Humeral Shaft Fracture

Mechanism

- direct blows/MVA (most common), FOOSH, twisting injuries, metastases (in elderly)

Clinical Features

- pain, swelling, \pm shortening, motion/crepitus at fracture site
- must test radial nerve function before and after treatment

Investigations

- x-rays: AP and lateral radiographs of the humerus including the shoulder and elbow joints

Treatment

- in general, humeral shaft fractures are treated non-operatively
- non-operative (most common)
 - \pm reduction – can accept deformity due to compensatory range of motion of shoulder
 - hanging cast (weight of arm in cast provides traction across fracture site) with sling immobilization x 7-10 days, then Sarmiento functional brace
- operative
 - indications: open fracture, neurovascular injury, unacceptable fracture alignment, polytrauma, segmental fracture, pathological fracture, “floating elbow” (simultaneous unstable humeral and forearm fractures), intra-articular
 - procedure: compression plating (most common), intramedullary rod insertion, external fixation

Specific Complications (see *General Fracture Complications*, OR6)

- radial nerve injury: expect spontaneous recovery in 3-4 months, otherwise send for electromyography (EMG)
- decreased ROM
- compartment syndrome



Acceptable Humeral Shaft Deformities for Non-operative Treatment

- $<20^\circ$ anterior angulation
- $<30^\circ$ varus angulation
- <3 cm of shortening



Risk of radial n. and brachial a. injury!

Elbow

General Principles

- articulation between distal humerus, proximal ulna, proximal radius (humeroradial, humeroulnar and radioulnar joints)
- fractures and dislocations of the elbow are evident on AP, lateral and oblique radiographs

Supracondylar Fracture

- most common in pediatric population (peak age ~7 years old), rarely seen in adults
- anterior interosseous nerve (AIN) injury commonly associated with extension type

Mechanism

- $>96\%$ are extension injuries via FOOSH (e.g. fall off monkey bars); $<4\%$ are flexion injuries

Clinical Features

- pain, swelling, point tenderness
- neurovascular injury – assess median and radial nerve, radial artery

Investigations

- x-rays: AP, lateral of elbow; assess for fat pad sign

Treatment

- non-operative
 - nondisplaced: cast in 90° flexion for 3 weeks
- operative
 - indications: displaced, vascular injury, open fracture
 - requires percutaneous pinning followed by limb cast with elbow flexed $>90^\circ$
 - in adults, ORIF is necessary

Specific Complications (see *General Fracture Complications*, OR6)

- brachial artery injury, median or ulnar nerve injury, compartment syndrome (leads to Volkmann's ischemic contracture), malalignment cubitus varus (distal fragment tilted into varus)

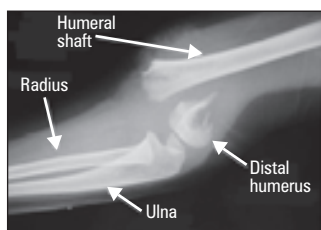


Figure 21. X-Ray of Transverse Displaced Supracondylar Fracture of Humerus with Elbow Dislocation

Radial Head Fracture

- a common fracture of the upper limb in young adults

Mechanism

- FOOSH with elbow extended and forearm pronated

Clinical Features

- marked local tenderness on palpation over radial head (lateral elbow)
- decreased ROM at elbow, mechanical block to forearm pronation and supination
- pain on pronation/supination

Investigations

- x-ray: enlarged anterior fat pad ("sail sign") or the presence of a posterior fat pad indicate occult radial head fractures

Table 8. Classification and Treatment of Radial Head Fractures

Mason Class	Radiographic Description	Treatment
1	Undisplaced fracture	Elbow slab or sling x 3-5 days with early ROM
2	Displaced fracture	ORIF if: angulation $>30^\circ$, involves $\geq 1/3$ of the radial head, or if ≥ 3 mm of joint incongruity exists
3	Comminuted fracture	Radial head excision \pm prosthesis
4	Comminuted fracture with posterior elbow dislocation	Radial head excision \pm prosthesis

Specific Complications (see *General Fracture Complications*, OR6)

- myositis ossificans
- recurrent instability (if medial collateral ligament injured and radial head excised)

Olecranon Fracture

Mechanism

- direct trauma to posterior aspect of elbow (fall onto the point of the elbow)

Clinical Features

- \pm loss of active extension due to avulsion of triceps tendon

Treatment

- undisplaced (<2 mm, stable): cast x 3 weeks (elbow in 45° flexion) then gentle ROM
- displaced: ORIF (plate and screws or tension band wiring) and early ROM if stable

Elbow Dislocation

- third most common joint dislocation after shoulder and patella
- most commonly occurs in young people (5-25 years) in sporting events or high speed MVAs, dislocation of ulna
- 90% are posterior/posterolateral, anterior are rare
- collateral ligaments disrupted

Mechanism

- elbow hyperextension via FOOSH or valgus/supination stress during elbow flexion

Clinical Features

- elbow pain, swelling, deformity
- flexion contracture
- \pm absent radial or ulnar pulses

Treatment

- closed reduction under anesthesia (post-reduction x-rays required)
- long-arm splint with forearm in neutral rotation and elbow in 90° flexion
- early ROM (<2 weeks)

Specific Complications (see *General Fracture Complications*, OR6)

- stiffness (loss of extension), intra-articular loose body, neurovascular injury (ulnar nerve, median nerve, brachial artery), radial head fracture



Terrible Triad

1. Radial head fracture
2. Coronoid fracture
3. Elbow dislocation

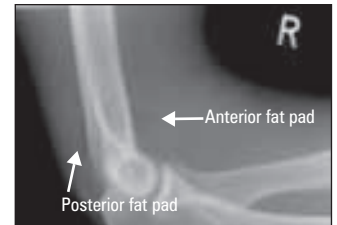


Figure 22. X-Ray of Fat-Pad Sign



Do not immobilize elbow joint
 $>2-3$ weeks to avoid stiffness.

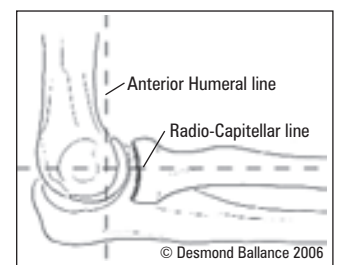


Figure 23. Lateral View of Elbow

Epicondylitis

- lateral epicondylitis = “tennis elbow”, inflammation of the common extensor tendon as it inserts into the lateral epicondyle
- medial epicondylitis = “golfer’s elbow”, inflammation of the common flexor tendon as it inserts into the medial epicondyle

Mechanism

- repeated or sustained contraction of the forearm muscles

Clinical Features

- point tenderness over humeral epicondyle
- pain upon resisted wrist extension (lateral epicondylitis) or wrist flexion (medial epicondylitis)
- generally a self-limited condition, but may take 6-18 months to resolve

Treatment

- rest, ice, NSAIDs
- use brace/strap
- PT, stretching and strengthening
- corticosteroid injection
- surgery: percutaneous or open release of common tendon from epicondyle (only after 6-12 months of conservative therapy)

Forearm

Radius and Ulna Fracture

Mechanism

- commonly a FOOSH or direct blow

Investigations

- x-ray: 1) AP and lateral of forearm; 2) AP, lateral, oblique of elbow and wrist
- CT if fracture is close to joint

Treatment

- goal is anatomic reduction since imperfect alignment significantly limits forearm pronation and supination
- ORIF with compression plates and screws

Complications (see *General Fracture Complications*, OR6)

Monteggia Fracture

Definition

- fracture of the proximal ulna with radial head dislocation

Mechanism

- direct blow on the posterior aspect of the forearm
- hyperpronation
- fall on the hyperextended elbow

Clinical Features

- decreased rotation of forearm \pm palpation lump at the radial head
- ulna angled apex anterior and radial head dislocated anteriorly (rarely the reverse deformity occurs)

Treatment

- ORIF of ulna with indirect radius reduction in 90%
- splint and early post-op ROM if elbow completely stable; otherwise immobilization in plaster with elbow flexed for 6 weeks

Specific Complications (see *General Fracture Complications*, OR6)

- compartment syndrome
- radial/posterior interosseous nerve (PIN) injury
- decreased ROM

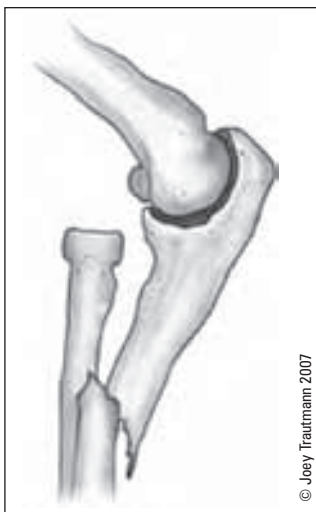


Figure 24. Monteggia Fracture



In all isolated ulna fractures, assess proximal radius to rule out a Monteggia fracture.

Nightstick Fracture

Definition

- isolated fracture of ulna

Mechanism

- direct blow to forearm (holding arm up to protect face)

Treatment

- non-displaced: below elbow cast (10 days) followed by forearm brace (~8 weeks)
- displaced: ORIF if >50% shaft displacement or >10° angulation

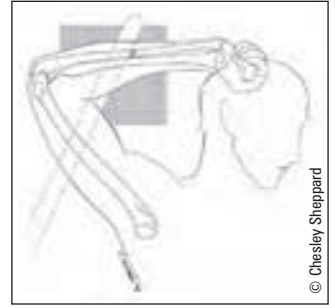


Figure 25. Nightstick Fracture

Galeazzi Fracture

Definition

- fracture of the distal radial shaft with disruption of the distal radioulnar joint (DRUJ)
- most commonly in the distal 1/3 of radius near junction of metaphysis/diaphysis

Mechanism

- usual cause is fall on the hand (mechanical axial loading of pronated forearm)

Investigations

- x-rays
 - shortening of distal radius >5 mm relative to the distal ulna
 - widening of the DRUJ space on AP
 - dislocation of radius with respect to ulna on true lateral

Treatment

- ORIF of radius
- if DRUJ is stable, splint with early ROM
- if DRUJ is unstable, DRUJ pinning and long arm cast in supination x 6 weeks

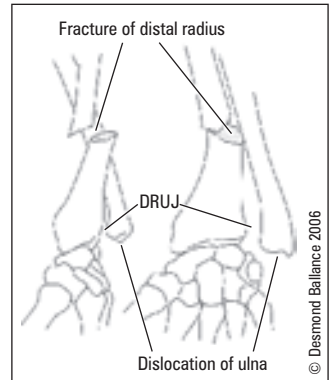


Figure 26. Galeazzi Fracture



For all isolated radius fractures assess DRUJ to rule out a Galeazzi fracture.

Wrist

Colles' Fracture

Definition

- transverse distal radius fracture (about 2 cm proximal to the radiocarpal joint) with dorsal displacement ± ulnar styloid fracture

Epidemiology

- most common fracture in those >40 years, especially in women and those with osteoporotic bone

Mechanism

- FOOSH

Clinical Features

- "dinner fork" deformity
- swelling, ecchymosis, tenderness

Investigations

- findings on x-ray (Figure 27)

Treatment

- goal is to restore radial height, radial inclination (22°), volar tilt (11°) and articular congruity
- closed reduction (think opposite of the deformity):
 - hematoma block (sterile prep and drape, local anesthetic injection directly into fracture site) or conscious sedation
 - closed reduction – traction with extension (exaggerate injury), then traction with ulnar deviation, pronation, flexion of distal fragment – not at wrist)
 - dorsal slab/below elbow cast for 5-6 weeks
 - x-ray q1 week to ensure reduction is maintained
- obtain post-reduction films immediately; repeat reduction if necessary, consider external fixation or ORIF

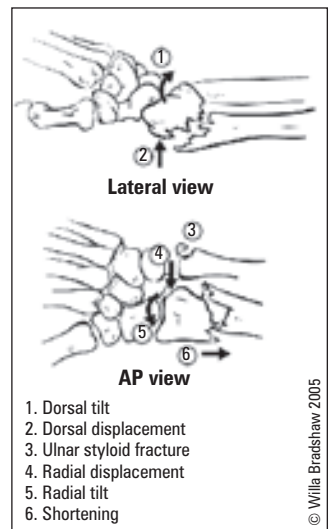


Figure 27. Colles' Fracture and Associated Bony Deformity

Smith's Fracture

Definition

- volar displacement of the distal radius (i.e. reverse Colles' fracture)

Mechanism

- fall onto the back of the flexed hand

Treatment

- usually unstable and needs ORIF
- if patient is poor operative candidate, may attempt non-operative treatment
- closed reduction with hematoma block (reduction opposite of Colles')
- long-arm cast in supination x 6 weeks



Complications of Wrist Fractures

- most common complications are poor grip strength, stiffness, and radial shortening
- distal radius fractures in individuals <40 years of age are usually highly comminuted and are likely to require ORIF
- 80% have normal function in 6-12 months
- early
 - difficult reduction \pm loss of reduction
 - compartment syndrome
 - extensor pollicis longus (EPL) tendon rupture
 - acute carpal tunnel syndrome
 - finger swelling with venous or lymphatic block
- late
 - mal-union, radial shortening
 - painful wrist secondary to ulnar prominence
 - frozen shoulder ("shoulder-hand syndrome")
 - post-traumatic arthritis
 - carpal tunnel syndrome
 - complex regional pain syndrome (reflex sympathetic dystrophy (RSD))



Scaphoid Fracture

Epidemiology

- common in young men; not common in children or in patients beyond middle age

Mechanism

- FOOSH resulting most commonly in a transverse fracture through the waist (middle) of the scaphoid

Clinical Features

- pain on wrist movement
- tenderness in scaphoid region (anatomical "snuff box")
- usually undisplaced

Investigations

- x-ray: AP, lateral, scaphoid views with wrist extension and ulnar deviation q2 weeks
- \pm bone scan
- \pm CT, MRI
- **Note:** a fracture may not be radiologically evident up to 2 weeks after acute injury, so if a patient complains of wrist pain and has anatomical snuff box tenderness but a negative x-ray, treat as if positive for a scaphoid fracture and repeat x-ray 2 weeks later to rule out a fracture. If x-ray still negative order CT or MRI

Treatment

- non-displaced = long-arm thumb spica cast x 4 weeks then short arm cast until radiographic evidence of healing is seen (2-3 months)
- displaced = open (or percutaneous) screw fixation

Specific Complications (see *General Fracture Complications*, OR6)

- AVN of the proximal fragment (since the scaphoid has distal to proximal blood supply, the more proximal the fracture, the greater incidence of AVN)
- delayed union (recommend surgical fixation)
- non-union (must use bone graft and fixation to heal)

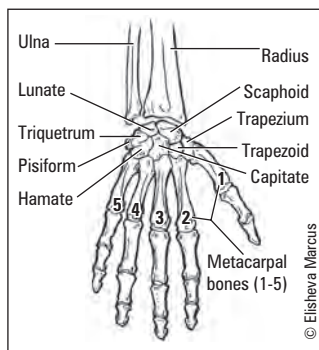


Figure 28. Carpal Bones



Figure 29. ORIF Left Scaphoid

Prognosis

- fractures of the proximal third of the scaphoid have 70% rate of non-union or AVN
- waist fractures have healing rates of 80-90%
- distal third fractures have healing rates close to 100%

Hand

- see [Plastic Surgery](#), PL20

Evaluation of Hand Complaints

History

- hand dominance, AM stiffness, location of pain, swelling, mass, trauma, activity, neurological symptoms, history of arthritis

Physical Examination

- deformities
 - fracture: rotational or angular
 - rheumatoid arthritis: ulnar deviation, swan neck, boutonniere, mallet finger
- finger position
 - Dupuytren's contracture: flexion contracture of 4th/5th finger
- swelling/masses
 - Heberden's node: DIP swelling
 - Bouchard's node: PIP swelling
 - rheumatoid arthritis: MCP swelling
- skin changes
- nail changes: clubbing, koilonychia, leukonychia, Lindsay's nails, Terry's nails, onycholysis
- muscle wasting: thenar, hypothenar, intrinsic
- range of motions, crepitus, joint line tenderness, joint stability
- all bones, including carpal bones, can be palpated to identify maximum tenderness
- neurovascular examination

Special Tests of the Hand

- test of flexor digitorum profundus
 - flex DIP while holding MCP in extension
 - if unable to flex DIP, then suggestive of flexor digitorum profundus pathology
- test of flexor digitorum superficialis (sublimes)
 - flex PIP while holding MCP in extension
 - if unable to flex PIP only, then suggestive of flexor digitorum superficialis pathology
- test of thumb instability
 - apply a valgus stress to thumb while stabilizing metacarpal; keep MCP flexed slightly while testing
 - if there is laxity in thumb, then suggestive of ulnar collateral ligament rupture
- test of finger instability
 - apply varus and valgus stress to finger while stabilizing PIP
 - if there is laxity in PIP, then suggestive of collateral ligament damage
- Allen's test
 - occlude both ulnar and radial artery; release one at a time to determine patency of each artery
- Finklestein's test
 - place thumb in palm and cover with all fingers and move wrist into ulnar deviation
 - if pain is reproduced at radial styloid region, then suggestive of tenosynovitis of 1st compartment (EPB, APL tendons)
- test of carpal tunnel syndrome
 - see [Plastic Surgery](#), PL25

Spine

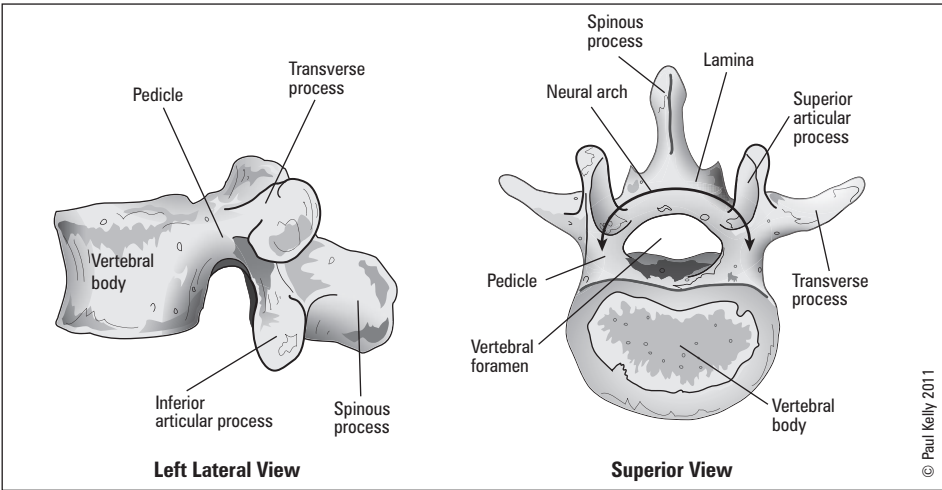


Figure 30. Schematic Diagram of Vertebral Anatomy
Adapted from Moore's Clinical Anatomy, Page 274 – A&D

Fractures of the Spine

- see [Neurosurgery](#), NS34
- 4 main types of fractures (see Table 9)

Table 9. Fracture Type and Column Involvement

Fracture Type	Column Failure	Stable/Unstable	Mechanism
Compression	Anterior	Stable	Compression
Burst	Anterior, middle	± Unstable	High-energy axial loading + flexion
Flexion-distraction	Middle, posterior	± Unstable	MVA (lap belt only) causing flexion and distraction (Chance fracture)
Fracture-dislocation	Anterior, middle, posterior	Unstable	Significant force applied to spine (flexion, extension, distraction, rotation, shear or axial load)

Cervical Spine

General Principles

- C1 = atlas: no vertebral body, no spinous process
- C2 = axis: odontoid = dens
- 7 cervical vertebrae; 8 cervical nerve roots
- nerve root exits above vertebra (i.e. C4 nerve root exits above C4 vertebra)
- radiculopathy = impingement of nerve root
- myelopathy = impingement of spinal cord

Special Testing

- Compression test: pressure on head worsens radicular pain
- Distraction test: traction on head relieves radicular symptoms
- Valsalva test: Valsalva maneuver increases intrathecal pressure and causes radicular pain

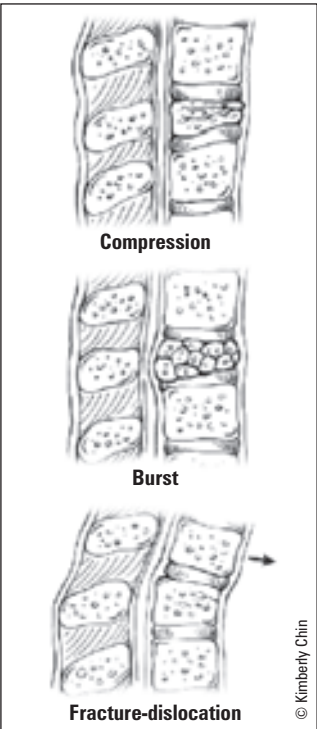


Figure 31. Burst, Compression and Dislocation Fracture

Table 10. Cervical Radiculopathy/Neuropathy

Root	C5	C6	C7	C8
Motor	Deltoid Biceps Wrist extension	Biceps Brachioradialis	Triceps Wrist flexion Finger extension	Interossei Digital flexors
Sensory	Axillary nerve (patch over lateral deltoid)	Thumb and index finger	Middle finger	Ring and little finger
Reflex	Biceps	Biceps Brachioradialis	Triceps	Finger jerk

X-Rays for C-Spine

- AP spine: alignment
- AP odontoid: atlantoaxial articulation
- lateral
 - vertebral alignment: posterior vertebral bodies should be aligned (translation >3.5 mm is abnormal)
 - angulation: between adjacent vertebral bodies (>11° is abnormal)
 - disc or facet joint widening
 - anterior soft tissue space (at C3 should be ≤3 mm; at C4 should be ≤8-10 mm)
- oblique: evaluate pedicles and intervertebral foramen
- ± swimmer's view: lateral view with arm abducted 180° to evaluate C7-T1 junction if lateral view is inadequate (must see C7-T1 in all trauma situations)
- ± lateral flexion/extension view: evaluate subluxation of cervical vertebrae

Differential Diagnosis of C-Spine Pain

- trapezial sprain, whiplash, cervical spondylosis, cervical stenosis, rheumatoid arthritis (spondylitis), traumatic injury

C-SPINE INJURY

- see [Neurosurgery](#), NS34

Thoracolumbar Spine**General Principles**

- spinal cord terminates at conus medullaris (L1)
- individual nerve roots exit below pedicle of vertebra (i.e. L4 nerve root exits below L4 pedicle)

Special Tests

- Straight leg raise (SLR): passive lifting of leg (30-70°) reproduces radicular symptoms of pain radiating down post/lat leg to knee, ± into foot
- Lasegue maneuver: dorsiflexion of foot during SLR makes symptoms worse or, if leg is less elevated, dorsiflexion will bring on symptoms
- Femoral stretch test: with patient prone, flexing the knee of the affected side and passively extending the hip results in radicular pain

Table 11. Lumbar Radiculopathy/Neuropathy

Root	L4	L5	S1
Motor	Quadriceps (knee extension + hip adduction) Tibialis anterior (ankle inversion + dorsiflexion)	EHL (extensor hallucis longus) Gluteus medius (hip abduction)	Peroneus longus + brevis (ankle eversion) Gastrocnemius + soleus (plantar flexion)
Sensory	Medial malleolus	1st dorsal webspace and lateral leg	Lateral foot
Reflex	Knee (Patellar)	Medial hamstring*	Ankle (Achilles)
Test	Femoral stretch	Straight leg raise	Straight leg raise

*Unreliable

**Red Flags for BACK PAIN**

Bowel or bladder dysfunction
Anesthesia (saddle)
Constitutional symptoms/malignancy
Chronic disease
Paresthesias
Age >50
IV drug use
Neuromotor deficits

**Canadian C-spine Rule (CCR)**

Used to guide imaging for alert (GCS = 15) and stable patients with suspected C-spine injury
Obtain radiography if:

- Age >65
- Paresthesia in the extremities
- Inability to rotate neck >45°
- Dangerous mechanism of injury (e.g. high speed MVA, fall from elevation > 5 ft, etc.)

Reference: *CJEM* 2002;4(2):84-90

Immediate immobilization of C-spine at scene of accident with spine board, C-collar and sandbags.



Cauda equina syndrome and ruptured aortic aneurysms are causes of low back pain that are considered surgical emergencies.

Differential Diagnosis of Back Pain

1. mechanical or nerve compression (>90%)
 - degenerative (disc, facet, ligament)
 - peripheral nerve compression (disc herniation)
 - spinal stenosis (congenital, osteophyte, central disc)
 - cauda equina syndrome
2. others
 - neoplastic (primary, metastatic, multiple myeloma)
 - infectious (osteomyelitis, TB)
 - metabolic (osteoporosis)
 - traumatic fracture (compression, distraction, translation, rotation)
 - spondyloarthropathies (ankylosing spondylitis)
 - referred (aorta, renal, ureter, pancreas)

DEGENERATIVE DISC DISEASE

- loss of vertebral disc height with age results in:
 - bulging and tears of annulus fibrosus
 - change in alignment of facet joints
 - osteophyte formation
- can cause back-dominant pain
- management
 - non-operative
 - ♦ staying active with modified activity
 - ♦ back strengthening
 - ♦ NSAIDs
 - ♦ do not treat with opioids; no proven efficacy of spinal traction or manipulation
 - operative – rarely indicated
 - ♦ decompression ± fusion
 - ♦ no difference in outcome between non-operative and surgical management at 2 years

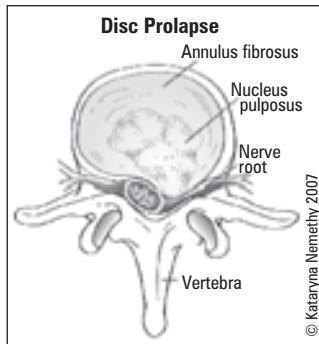


Figure 32. Disc Herniation

Table 12. Types of Low Back Pain

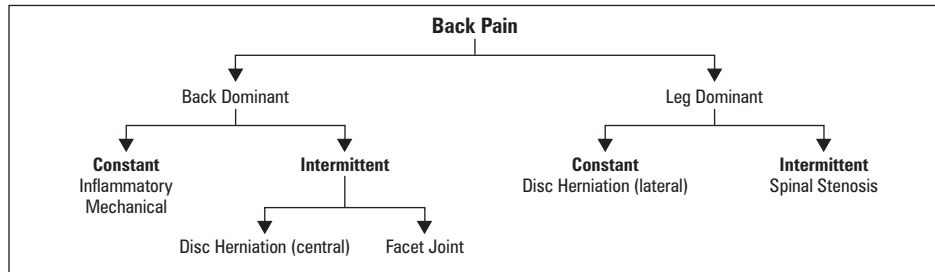
	Mechanical Back Pain		Direct Nerve Root Compression	
	Disc Origin	Facet Origin	Spinal Stenosis	Root Compression
Pain Dominance	Back	Back	Leg	Leg
Aggravation	Flexion	Extension Standing, walking	Exercise, extension, walking, standing	Flexion
Onset	Gradual	More sudden	Congenital or acquired	Acute leg ± back pain
Duration	Long (weeks, months)	Shorter (days, weeks)	Acute or chronic history (weeks to months)	Short episodes Attacks (minutes)
Treatment	Relief of strain, exercise	Relief of strain, exercise	Relief of strain, exercise	Relief of strain, exercise + surgical decompression if progressive or severe deficit

SPINAL STENOSIS

- definition: narrowing of spinal canal <10 mm
- etiology: congenital (idiopathic, osteopetrosis, achondroplasia) or acquired (degenerative, iatrogenic – post spinal surgery, ankylosing spondylosis, Paget's disease, trauma)
- clinical features
 - ± bilateral back and leg pain
 - neurogenic claudication (see Table 13)
 - ± motor weakness
 - normal back flexion; difficulty with back extension
- investigations: CT/MRI reveals narrowing of spinal canal, but gold standard = CT myelogram
- treatment
 - non-operative: vigorous PT (flexion exercises, stretch/strength exercises), NSAIDs, lumbar epidural steroids
 - operative: decompression surgery if conservative methods failed >6 months

Table 13. Differentiating Claudication

	Neurogenic	Vascular
Aggravation	With standing or exercise Walking distance variable	Walking set distance
Alleviation	Change in position (usually flexion, sitting, lying down)	Stop walking
Time	Relief in ~10 min	Relief in ~2 min
Character	Neurogenic \pm neurological deficit	Muscular cramping

**Figure 33. Approach to Back Pain**

MRI abnormalities are quite common in both asymptomatic and symptomatic individuals and are not necessarily an indication for intervention without clinical correlation.

MECHANICAL BACK PAIN

- definition: back pain NOT due to prolapsed disc or any other clearly defined pathology
- clinical features
 - dull backache aggravated by activity
 - morning stiffness
 - no neurological signs
- treatment: symptomatic (analgesics, PT)
- prognosis: symptoms may resolve in 4-6 weeks, others become chronic

LUMBAR DISC HERNIATION

- definition: tear in annulus fibrosus allows protrusion of nucleus pulposus causing either a central, posterolateral or lateral disc herniation, most commonly at L5-S1 > L4-5 > L3-4
- etiology: usually a history of flexion-type injury which tears the annulus fibrosus allowing for protrusion of the nucleus pulposus
- clinical features
 - back dominant pain (central herniation) or leg dominant pain (lateral herniation)
 - tenderness between spines at affected level
 - muscle spasm \pm loss of normal lumbar lordosis
 - neurological disturbance is segmental and varies with level of central herniation
 - ♦ motor weakness (L4, L5, S1)
 - ♦ diminished reflexes (L4, S1)
 - ♦ diminished sensation (L4, L5, S1)
 - +ve straight leg raise
 - +ve Lasague test
 - bowel or bladder symptoms, decreased rectal tone suggests cauda equina syndrome due to central disc herniation – surgical emergency
- investigations: MRI
- treatment
 - symptomatic
 - ♦ extension protocol (PT)
 - ♦ NSAIDs
 - ♦ 90% resolve in 3 months
 - surgical discectomy reserved for progressive neurological deficit, failure of symptoms to resolve within 3 months or cauda equina syndrome due to central disc herniation

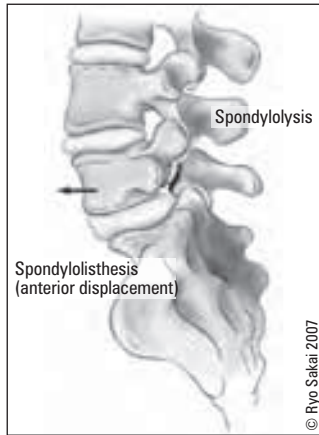


Figure 34. Spondylolysis, Spondylolisthesis

SPONDYLOLYSIS

- definition: defect in the pars interarticularis with no movement of the vertebral bodies
- etiology
 - trauma: gymnasts, weightlifters, backpackers, loggers, labourers
- clinical features: activity-related back pain
- investigations
 - oblique x-ray: "collar" break in the "Scottie dog's" neck
 - bone scan
 - CT scan
- treatment: activity restriction, brace, stretching exercise

SPONDYLOLISTHESIS

- definition: defect in pars interarticularis causing a forward slip of one vertebrae on another usually at L5-S1, less commonly at L4-5
- etiology: congenital (children), degenerative (adults), traumatic, pathological, teratogenic
- clinical features: lower back pain radiating to buttocks

Table 14. Classification and Treatment of Spondylolisthesis

Class	Percentage of Slip	Treatment
1	0-25%	Symptomatic operative fusion only for intractable pain
2	25-50	
3	50-75	Decompression for spondylolisthesis and spinal fusion
4	75-100	
5	>100	

Specific Complications

- may present as cauda equina syndrome due to roots being stretched over the edge of L5 or sacrum

Hip

Hip Fracture

General Features

- acute onset of hip pain
- unable to weight-bear
- shortened and externally rotated leg
- painful ROM

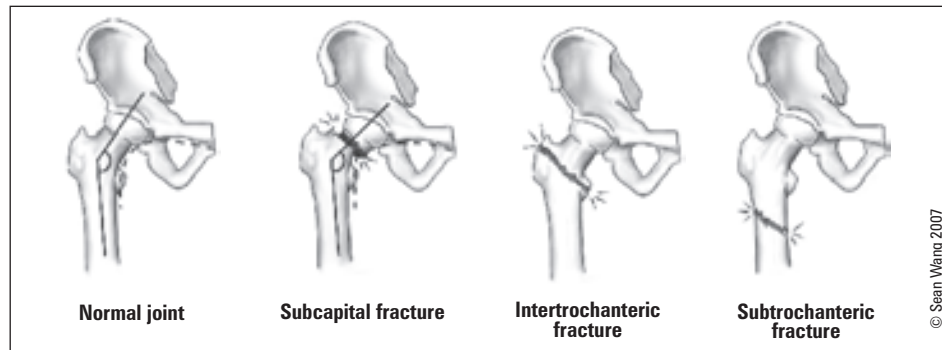


Figure 35. Subcapital, Intertrochanteric, Subtrochanteric Fractures

X-Ray Features of Subcapital Hip Fractures

- Disruption of Shenton's line (a radiographic line drawn along the upper margin of the obturator foramen, extending along the inferomedial side of the femoral neck)
- Altered neck-shaft angle (normal is 120-130°)

DVT Prophylaxis in Hip Fractures
LMWH (i.e. enoxaparin 40 mg SC bid) on admission, do not give <12 hrs before surgery.

Table 15. Overview of Hip Fractures

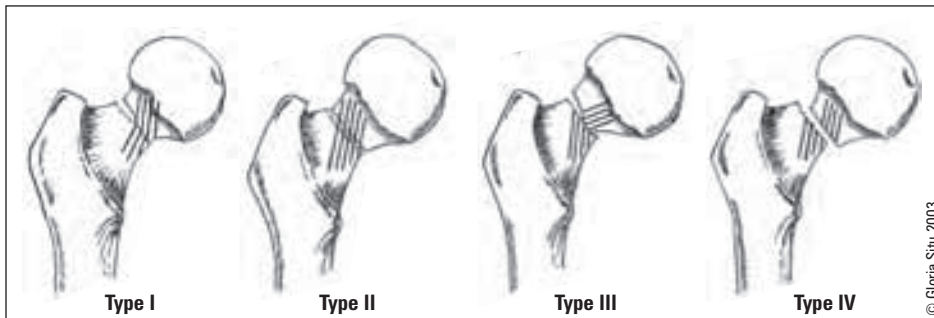
Fracture Type	Definition	Mechanism	Special Clinical Features	Investigations	Treatment	Complications
Femoral Neck (Subcapital)	Intracapsular (See Garden Classification, Table 16)	Young: MVA, fall from height Elderly: Fall from standing, rotational force	Same as general	X-ray: AP hip, AP pelvis, cross table lateral hip	See Table 16	DVT, Non-union
Intertrochanteric Fracture	Extracapsular fracture including the greater and lesser trochanters and transitional bone between the neck and shaft	Direct or indirect force transmitted to the intertrochanteric area	Ecchymosis at back of upper thigh	X-ray: AP pelvis, AP/lateral hip	Closed reduction under fluoroscopy then dynamic hip screw or IM nail	DVT, varus displacement of prox. fragment, malrotation, non-union, failure of fixation device
Subtrochanteric Fractures	Fracture begins at or below the lesser trochanter and involves the proximal femoral shaft	Young = high energy trauma Older = osteopenic bone + fall, pathological fracture	Ecchymosis at back of upper thigh	X-ray: AP pelvis, AP/lateral hip	Closed reduction under fluoroscopy then plate fixation or IM nail	Malalignment, non-union, wound infection

Table 16. Garden Classification of Femoral Neck Fractures

Type	Displacement	Extent	Alignment	Trabeculae	Treatment
I	None	Incomplete	Valgus	Malaligned	Internal fixation to prevent displacement
II	None	Complete	Neutral	Aligned	Internal fixation to prevent displacement
III	Some	Complete	Varus	Malaligned	Elderly: Hemi-/total hip arthroplasty Young: ORIF
IV	Complete	Complete	Varus	Aligned	Elderly: Hem-/total hip arthroplasty Young: ORIF

**AVN of Femoral Head**

- Distal to proximal blood supply along femoral neck to head (medial femoral circumflex artery)
- Susceptible to AVN if blood supply disrupted
- Etiology: femoral neck fracture, chronic systemic steroid use

**Figure 36. Garden Classification of Femoral Neck Fractures**

Arthritis of the Hip

Etiology

- osteoarthritis (OA), inflammatory arthritis, post-traumatic arthritis, late effects of congenital hip disorders or septic arthritis

Clinical Features

- pain (groin, medial thigh) and stiffness aggravated by activity
- morning stiffness, multiple joint swelling, hand nodules (RA)
- decreased ROM (internal rotation is lost first)
- crepitus
- \pm fixed flexion contracture leading to apparent limb shortening (Thomas test)
- \pm Trendelenberg sign

Investigations

- x-ray
 - OA: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes
 - RA: osteopenia, joint space narrowing, subchondral cysts
- bloodwork: ANA, RF

**DVT Prophylaxis in Elective THA**
(continue 2-3 weeks post-op)

Low molecular weight heparin or coumadin.

Treatment

- conservative: weight reduction, activity modification, PT, analgesics, walking aids
- operative: realign = osteotomy; replace = arthroplasty; fuse = arthrodesis
- complications with arthroplasty: component loosening, dislocation, heterotopic bone formation, thromboembolus, infection, neurovascular injury
- arthroplasty is standard of care in most patients with hip arthritis

Hip Dislocation after THA

Etiology

- total hip arthroplasty (THA) that is unstable when hip is flexed, adducted and internally rotated or extended and externally rotated (avoid flexing hip >90 degrees or crossing legs for approximately 6 weeks after surgery)

Epidemiology

- occurs in 1-4% of primary THA and 10-16% of revision THAs
- risk factors: neurological impairment, post-traumatic arthritis, revision surgery, substance abuse

Treatment

- external abduction splint to prevent hip adduction
- constrained acetabular component for recurrent dislocation if no issue with position of acetabular/femoral implants

Complications

- sciatic nerve palsy in 25% (10% permanent)
- heterotopic ossification (HO)

Femur

Femoral Diaphysis Fracture

Mechanism

- high energy trauma (MVA, fall from height, gunshot wound)
- in children, can result from low energy trauma (spiral fracture)

Clinical Features

- shortened, externally rotated leg (if fracture displaced)
- inability to weight-bear
- often open injury, always a Gustilo III

Investigations

- AP pelvis, AP/lateral hip, femur, knee

Specific Complications

- hemorrhage requiring transfusion
- fat embolism leading to ARDS
- extensive soft tissue damage
- ipsilateral hip dislocation/fracture
- nerve injury

Treatment

- stabilize patient
- immobilize leg
- ORIF with intramedullary nail, external fixator, or plate and screws within 24 hours
- early mobilization and strengthening

Distal Femoral Fracture

Mechanism

- direct high energy force or axial loading
- three types (Figure 37)

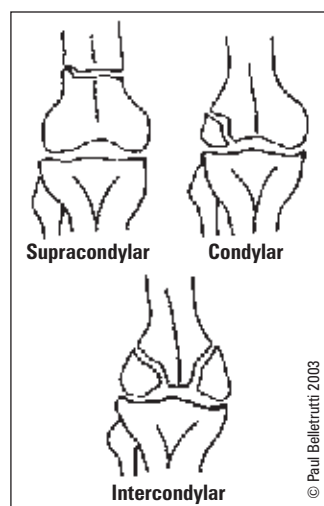


Figure 37. Distal Femoral Fractures

Clinical Features

- direct high energy force or axial loading
- extreme pain
- knee effusion (hemarthrosis)
- shortened, externally rotated leg if displaced

Treatment

- ORIF
- early mobilization and strengthening

Complications (see *General Fracture Complications*, OR6)

- femoral artery tear
- nerve injury
- extensive soft tissue injury
- angulation deformities

Knee

Evaluation of Knee Complaints

History

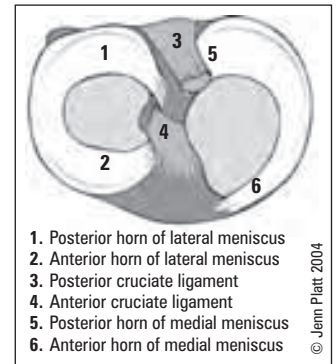
- general orthopaedic history
- also inquire about common knee symptoms
 - locking: mechanical block to extension
 - ♦ torn meniscus/loose body in joint
 - pseudo-locking: limited ROM without mechanical block
 - ♦ effusion, muscle spasm after injury, arthritis
 - painful clicking (audible)
 - ♦ torn meniscus
 - giving way: instability
 - ♦ cruciate ligament or meniscal tear, patellar dislocation

Physical Examination

- general orthopaedic physical exam (do not forget to evaluate hip)

Special Tests of the Knee

- **Anterior and Posterior drawer tests** (see Figure 39)
 - demonstrate torn ACL and PCL, respectively
 - knee flexed at 90°, foot immobilized, hamstrings released
 - if able to sublux tibia anteriorly, then ACL may be torn
 - if able to sublux tibia posteriorly, then PCL may be torn
- **Lachmann test**
 - demonstrates torn ACL
 - hold knee in 10-20° flexion, stabilizing the femur
 - try to sublux tibia anteriorly on femur
 - similar to anterior drawer test, more reliable due to less muscular stabilization
- **Posterior sag sign**
 - demonstrates torn PCL
 - may give a false positive anterior draw sign
 - flex knees and hips to 90°, hold ankles and knees
 - view from the lateral aspect
 - if one tibia sags posteriorly compared to the other, its PCL is torn
- **Pivot shift sign**
 - demonstrates torn ACL
 - start with the knee in extension
 - internally rotate foot, slowly flex knee while palpating and applying a valgus force
 - normal knee will flex smoothly
 - if incompetent ACL, tibia will sublux anteriorly on femur at start of maneuver. During flexion, the tibia will reduce and externally rotate about the femur (the "pivot")
 - reverse pivot shift (start in flexion, externally rotate, apply valgus and extend knee) suggests torn PCL
- **Collateral ligament stress test**
 - palpate ligament for "opening" of joint space while testing
 - with knee in full extension, apply valgus force to test MCL, apply varus force to test LCL
 - repeat tests with knee in 20° flexion to relax joint capsule
 - opening only in 20° flexion due to MCL damage only
 - opening in 20° of flexion and full extension is due to MCL, cruciate, and joint capsule damage

**Figure 38. Diagram of the Right Tibial Plateau****6 Degrees of Freedom of the Knee**

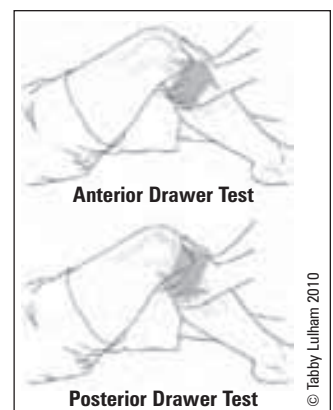
1. Flex. and ext.
2. Ext. and int. rotation
3. Varus and valgus angulation
4. Ant. and post. glide
5. Med. and lat. shift
6. Compression and distraction

**Knee History****CLIPS**

- Clicking
- Locking
- Instability
- Pain (location)
- Swelling



Physical examination difficult in acute knee injuries. Immobilize leg and re-examine in one week.

**Figure 39. Anterior and Posterior Drawer Test**

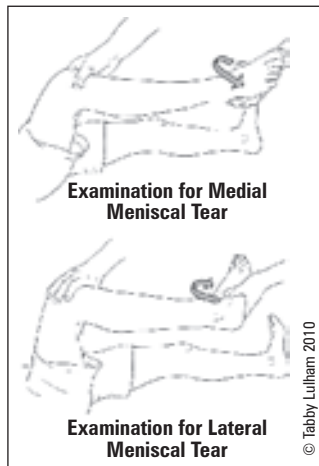


Figure 40. McMurray Test

- **Tests for meniscal tear**
 - Crouch compression test
 - ♦ joint line pain when squatting (anterior pain suggests patellofemoral pathology)
 - McMurray's test useful collaborative information (see Figure 40)
 - ♦ with knee in flexion, palpate joint line for painful "pop/click"
 - ♦ internally rotate foot, varus stress, and extend knee to test lateral meniscus
 - ♦ externally rotate foot, valgus stress, and extend knee to test medial meniscus

X-Rays

- AP standing, lateral
- skyline – tangential view with knees flexed at 45° to see patellofemoral joint
- 3-foot standing view – useful in evaluating leg length and varus/valgus alignment
- see Ottawa Knee Rules ([Emergency Medicine](#), ER17)

Cruciate Ligament Tears

- ACL tear much more common than PCL tear

Table 17. Comparison of ACL and PCL Injuries

	Anterior Cruciate Ligament	Posterior Cruciate Ligament
Mechanism	Sudden deceleration Hyperextension and internal rotation of tibia on femur	Sudden posterior displacement of tibia when knee is flexed or hyperextended (dashboard MVA injury)
History	Audible "pop" Immediate swelling Knee "giving way" Inability to continue activity	Audible "pop" Immediate swelling Pain with push off Cannot descend stairs
Physical	Effusion (hemarthrosis) Posterolateral joint line tenderness Positive anterior drawer Positive Lachmann Pivot shift Test for MCL, meniscal injuries	Effusion (hemarthrosis) Anteromedial joint line tenderness Positive posterior drawer Reverse pivot shift Other ligamentous, bony injuries
Treatment	Stable knee with minimal functional impairment: immobilization 2-4 weeks with early ROM and strengthening	Unstable knee or young person/high-demand lifestyle: ligament reconstruction Posterior sag



Figure 41. T1 MRI of Torn ACL

Collateral Ligament Tears

- MCL tear more common than LCL tear

Mechanism

- valgus force to knee = medial collateral ligament
- varus force to knee = lateral collateral ligament

Clinical Features

- swelling/effusion
- tenderness above and below joint line medially (MCL) or laterally (LCL)
- joint laxity with varus or valgus force to knee
 - laxity with endpoint suggests partial tear
 - laxity with no endpoint suggests a complete tear
- test for other injuries (e.g. O'Donahue's triad), common peroneal nerve injury

Treatment

- partial tear: immobilization x 2-4 weeks with early ROM and strengthening
- complete tear or multiple ligamentous injuries: surgical repair of ligaments – not for MCL or LCL on their own

Meniscal Tears

- medial tear much more common than lateral tear

Mechanism

- twisting force on knee when it is partially flexed (e.g. stepping down and turning)
- requires moderate trauma in young person but only mild trauma in elderly due to degeneration



Partial ligamentous tears are much more painful than complete ligamentous tears.



Tissue Sources for ACL Reconstruction

1. Hamstring
2. Middle 1/3 patellar tendon (bone-patellar-bone)
3. Allograft (e.g. cadaver)

Clinical Features

- immediate pain, difficulty weight-bearing, instability and clicking
- increased pain with squatting and/or twisting
- effusion (hemarthrosis) with insidious onset (24-48 hrs after injury)
- joint line tenderness medially or laterally
- locking of knee (if portion of meniscus mechanically obstructing extension)

Investigations

- MRI, arthroscopy

Treatment

- if not locked: ROM and strengthening
- if locked or failed above: arthroscopic repair/partial meniscectomy

Quadriceps/Patellar Tendon Rupture

Mechanism

- sudden forceful contraction of quadriceps during an attempt to stop
- more common in obese patients and those with pre-existing degenerative changes in tendon
 - DM, SLE, RA, steroid use, renal failure on dialysis

Clinical Features

- inability to extend knee or weight-bear
- possible audible “pop”
- patella in lower or higher position with palpable gap above or below patella respectively
- may have an effusion

Investigations

- ask patient to straight leg raise
- knee x-ray to rule out patellar fracture
- lateral view: patella alta with patella tendon rupture, patella baja with quadriceps tendon rupture

Treatment

- nonoperative treatment for incomplete tears with preserved extension of knee
- surgical repair of tendon indicated for complete ruptures

Dislocated Knee

Mechanism

- high energy trauma
- by definition, caused by tears of multiple ligaments

Clinical Features

- classified by relation of tibia with respect to femur
 - anterior, posterior, lateral, medial, rotary
- knee instability
- effusion
- pain
- ischemic limb

Investigations

- x-rays: AP, lateral, skyline
 - associated radiographic findings include tibial plateau fracture dislocations, proximal fibular fractures and avulsion of fibular head
- ankle brachial index (abnormal if less than 0.9)
- arteriogram if abnormal vascular exam

Treatment

- urgent closed reduction
 - complicated by interposed soft tissue
- assessment of peroneal nerve, tibial artery, and ligamentous injuries
- repair of associated injuries; also may need decompressive fasciotomy especially if vascular repair undertaken
- knee immobilization x 6-8 weeks

Specific Complications

- high incidence of associated injuries
 - popliteal artery tear
 - peroneal nerve injury
 - capsular tear
- chronic: instability, stiffness, post-traumatic arthritis

Patella

Patellar Fracture

Mechanism

- direct blow to the patella
- indirect trauma by sudden flexion of knee against contracted quadriceps

Clinical Features

- marked tenderness
- inability to extend knee or straight leg raise
- proximal displacement of patella
- patellar deformity
- \pm effusion

Investigations

- x-rays: AP, lateral, skyline
- consider bipartite patella: congenitally unfused ossification centres with smooth margins on x-ray

Treatment

- non-displaced (<2 mm)
 - straight leg immobilization 6-8 weeks
 - PT: quadriceps strengthening
- displaced: ORIF (>2 mm)
- comminuted: ORIF; may require partial/complete patellectomy

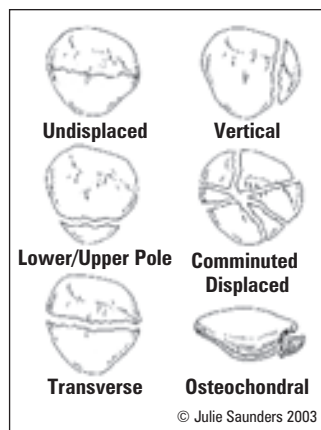


Figure 42. Types of Patellar Fractures



Patellar Dislocation

Mechanism

- lateral displacement of patella after contraction of quadriceps against a flexed knee

Risk Factors

- young, female
- obesity
- high-riding patella (patella alta)
- knock-knees (genu valgum)
- Q-angle (quadriceps angle) increased
- shallow intercondylar groove
- weak vastus medialis
- tight lateral retinaculum

Clinical Features

- knee catches or gives way with walking
- severe pain, tenderness anteromedially from rupture of capsule
- weak knee extension or inability to extend leg unless patella reduced
- +ve patellar apprehension test
 - patient apprehensive when examiner laterally displaces patella
- often recurrent, self-reducing

Investigations

- x-rays: AP, lateral, skyline view of patella
 - check for fracture of medial patella and lateral femoral condyle

Treatment

- non-operative first
 - knee immobilization x 4-6 weeks
 - progressive weight bearing and isometric quadriceps strengthening
- if recurrent
 - surgical tightening of medial capsule and release of lateral retinaculum, possible tibial tuberosity transfer, or proximal tibial osteotomy

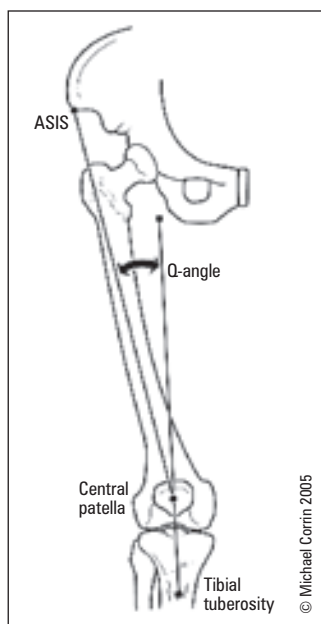


Figure 43. Q-Angle

Patellofemoral Syndrome (Chondromalacia Patellae)

Mechanism

- softening, erosion and fragmentation of articular cartilage, predominantly medial aspect of patella
- commonly seen in active young females
- predisposing factors
 - malalignment causing patellar maltracking (patellofemoral syndrome)
 - post-trauma
 - deformity of patella or femoral groove
 - recurrent patellar dislocation, ligamentous laxity
 - excessive knee strain (athletes)

Clinical Features

- deep, aching anterior knee pain
 - exacerbated by prolonged sitting (theatre sign), strenuous athletic activities, stair climbing, squatting
- sensation of instability, pseudolocking
- tenderness to palpation of underside of medially displaced patella
- pain with extension against resistance through terminal 30-40°
- swelling rare, minimal if present

Investigations

- x-rays: AP, lateral, skyline

Treatment

- non-operative
 - continue non-impact activities
 - NSAIDs
 - PT: quadriceps strengthening
- surgical with refractory patients
 - tibial tubercle elevation
 - arthroscopic shaving/debridement
 - lateral release of retinaculum



Pain with firm compression of patella into medial femoral groove is pathognomonic of chondromalacia patellae.

Tibia

Tibial Plateau Fracture

Mechanism

- axial loading (e.g. fall from height)
- femoral condyles driven into proximal tibia
- can result from minor trauma in osteoporotics

Clinical Features

- lateral fractures more common than medial

Classification

- Schatzker classification (see sidebar)

Investigations

- x-rays: AP, lateral, skyline

Treatment

- if depression on x-ray is <3 mm
 - straight leg immobilization x 4-6 weeks with progressive ROM weight bearing
- if depression is >3 mm
 - ORIF often requiring bone grafting to elevate depressed fragment

Specific Complications (see General Fracture Complications, OR6)

- ligamentous injuries
- meniscal lesions
- AVN
- infection



Schatzker Classification	
Type	Description
I	Involvement of lateral plateau split fracture
II	Involvement of lateral plateau: split depression fracture
III	Involvement of lateral plateau: pure depression fracture
IV	Medial plateau fracture
V	Bicondylar plateau fracture
VI	Bicondylar with metaphyseal/diaphyseal involvement



Tibial shaft fractures have high incidence of compartment syndrome and are often associated with soft tissue injuries.



Figure 44. Tibial Shaft Fracture Treated with Intra-medullary Nail and Screws

Tibial Shaft Fracture

Mechanism

- numerous, including MVA, falls, sporting injuries

Clinical Features

- open vs. closed
- amount of displacement
- neurovascular status
- most commonly fractured long bone
- most common open fracture

Investigations

- x-rays: AP, lateral, skyline

Treatment

- closed
 - minimally displaced: straight leg cast x 4-6 weeks with early weight bearing
 - displaced: ORIF with reamed IM nail, plate and screws, or external fixator
- open
 - external fixation or IM nail
 - vascularized coverage of soft tissue defects (often heal poorly)

Specific Complications (see *General Fracture Complications*, OR6)

- high incidence of neurovascular injury and compartment syndrome
- poor soft tissue coverage

Ankle

Evaluation of Ankle and Foot Complaints

Special Tests

- anterior drawer: examiner attempts to displace the foot anteriorly against a fixed tibia
- talar tilt: foot is stressed in inversion and angle of talar rotation is evaluated by x-ray

X-Ray

- AP, lateral
- mortise view: ankle at 15° of internal rotation
 - gives true view of ankle joint
 - joint space should be symmetric with no talar tilt
- Ottawa Ankle Rules should guide use of x-ray (see sidebar)
- ± CT to better characterize fractures



Ottawa Ankle Rules (see *Emergency Medicine*, ER17)

X-rays are only required if:
Pain in the malleolar zone AND bony tenderness over the posterior aspect of the medial or lateral malleolus
OR inability to weight bear both immediately after injury and in the E.R.

Ankle Fracture

Mechanism

- pattern of fracture depends on the position of the ankle when trauma occurs
- generally involves
 - ipsilateral ligamentous tears or transverse bony avulsion
 - contralateral shear fractures (oblique or spiral)
- classification systems
 - Danis-Weber (see below)
 - Lauge-Hansen: based on foot's position and motion relative to leg

Danis-Weber Classification (Figure 45)

- based on level of fibular fracture relative to syndesmosis
- **Type A** (infra-syndesmotom)
 - pure inversion injury
 - avulsion of lateral malleolus below plafond or torn calcaneofibular ligament
 - ± shear fracture of medial malleolus
- **Type B** (trans-syndesmotom)
 - external rotation and eversion (most common)
 - ± avulsion of medial malleolus or rupture of deltoid ligament
 - spiral fracture of lateral malleolus starting at plafond

- **Type C** (supra-syndesmotic)
 - pure external rotation
 - avulsion of medial malleolus or torn deltoid ligament
 - \pm posterior malleolus may be avulsed with posterior tibio-fibular ligament
 - fibular fracture is above plafond (called Maisonneuve fracture if at proximal fibula)
 - frequently tears syndesmosis

Treatment

- undisplaced: non-weight bearing below knee cast
- indications for ORIF
 - all fracture-dislocations
 - most of type B, and all of type C
 - trimalleolar (medial, posterior, lateral) fractures
 - talar tilt $>10^\circ$
 - medial clear space on XR greater than superior clear space
 - open fracture/open joint injury
- high incidence of post-traumatic arthritis

Ligamentous Injuries

Medial Ligament Complex (deltoid ligament)

- eversion injury
- usually avulses medial or posterior malleolus and strains syndesmosis

Lateral Ligament Complex (ATF, CF, PTF)

- inversion injury
- ATF most severely injured if ankle is plantar flexed
- swelling and tenderness anterior to lateral malleolus
- ++ ecchymoses
- +ve ankle anterior drawer
- may have significant medial talar tilt on inversion stress x-ray

Treatment

- microscopic tear (Grade I)
 - rest, ice, compression, elevation (RICE)
- macroscopic tear (Grade II)
 - strap ankle in dorsiflexion and eversion x 4-6 weeks
 - PT: strengthening and proprioceptive retraining
- complete tear (Grade III)
 - below knee walking cast 4-6 weeks
 - PT: strengthening and proprioceptive retraining
 - surgical intervention may be required if chronic symptomatic instability develops

Foot

Talar Fracture

Mechanism

- axial loading or hyperdorsiflexion (MVA, fall from a height)
- 60% of talus covered by articular cartilage
- tenuous blood supply runs distal to proximal along talar neck
 - high risk of AVN with displaced fractures

Investigations

- x-rays: AP, lateral
- CT to better characterize fracture
- MRI can clearly define extent of AVN

Treatment

- undisplaced: non-weight bearing below knee cast x 20-24 weeks
- displaced: ORIF (high rate of nonunion, AVN)

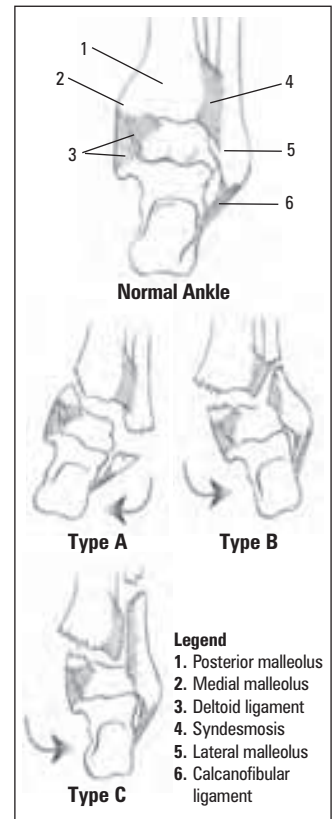


Figure 45. Ring Principle of the Ankle and Danis-Weber Classification

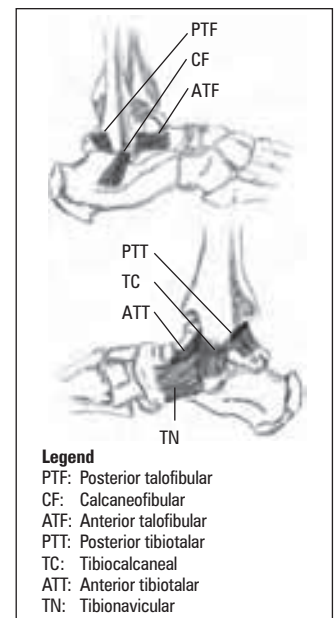


Figure 46. Ankle Ligament Complexes



With a history of trauma from axial loading of lower limb always consider spinal injuries, femoral neck, tibial plateau, talar/calcaneal fractures.

Calcaneal Fracture

Mechanism

- axial loading: fall from a height onto heels
- 10% of fractures associated with compression fractures of thoracic or lumbar spine
- 5% are bilateral

Physical Examination

- swelling, bruising on heel/sole
- wider, shortened, flatter heel when viewed from behind

Investigations

- x-rays: AP, lateral, oblique (Broden's view)
- loss of Bohler's angle
- CT – assess intraarticular extension

Treatment

- closed vs. open reduction is controversial
- non-weight bearing cast approximately 3 months with early ROM and strengthening



Calcaneal Fracture Treatment Principles

1. Avoid wound complications
2. Restore articular congruity
3. Restore normal calcaneal width and height
4. Maximum functional recovery may take longer than 12 months

Achilles Tendonitis

Mechanism

- chronic inflammation from activity or poor-fitting footwear
- may also develop heel bumps (retrocalcaneobursitis)

Physical Examination

- pain, stiffness and crepitus with ROM
- thickened tendon, palpable bump

Treatment

- rest, NSAIDs
- gentle stretching, deep tissue calf massage
- orthotics, open back shoes
- DO NOT inject steroids (risk of tendon rupture)

Achilles Tendon Rupture

Mechanism

- loading activity, stop-and-go sports (e.g. squash, tennis, basketball)
- secondary to chronic tendonitis, steroid injection

Clinical Features

- audible pop, sudden pain with push off movement
- sensation of being kicked in heel when trying to plantar flex
- palpable gap
- apprehensive toe off when walking
- weak plantar flexion, +ve Thompson test: with patient prone, squeezing the calf muscles should passively plantar flex the foot to demonstrate intact Achilles tendon
 - +ve test = no passive plantar flexion = ruptured tendon

Treatment

- low demand or elderly: cast foot in plantar flexion (to relax tendon) x 8-12 weeks
- high demand: surgical repair, then cast as above x 6-8 weeks



The most common site of Achilles tendon rupture is 2-6 cm from its insertion where the blood supply is the poorest.

Plantar Fasciitis (Heel Spur Syndrome)

Mechanism

- repetitive strain injury causing microtears and inflammation of plantar fascia
- female:male = 2:1
- common in athletes (especially runners)
- also associated with obesity, DM, seronegative and seropositive arthritis

Clinical Features

- morning pain and stiffness
- intense pain when walking from rest that subsides as patient continues to walk
- swelling, tenderness over sole
- greatest at medial calcaneal tubercle and 1-2 cm distal along plantar fascia
- pain with toe dorsiflexion (stretches fascia)

Investigations

- plain radiographs to rule out fractures
- often see exostoses (heel spurs) at insertion of fascia into medial calcaneal tubercle (see Figure 47)
- spur is reactive to inflammation, not the cause of pain

Treatment

- rest, ice, NSAIDs, steroid injection
- PT: stretching, ultrasound
- orthotics with heel cup
 - to counteract pronation and disperse heel strike forces
- endoscopic surgical release of fascia in refractory cases
 - spur removal is not required

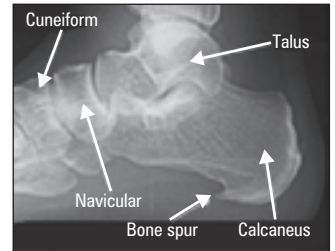


Figure 47. X-Ray of Bony Heel Spur

Bunions (Hallux Valgus)

Mechanism

- valgus alignment on 1st MTP (hallux valgus) causes eccentric pull of extensor and intrinsic muscles
- reactive exostosis forms with thickening of the skin creating a bunion
- most often associated with poor-fitting footwear but can be hereditary
- 10x more frequent in women

Clinical Features

- painful bursa over medial eminence of 1st metatarsal head
- pronation (rotation inward) of great toe
- numbness over medial aspect of great toe

Treatment

- cosmetic and to relieve pain
- non-operative first
 - properly fitted shoes (low heel) and toe spacer
- surgical
 - osteotomy with realignment of 1st MTP joint

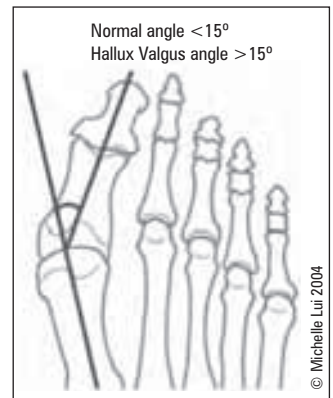


Figure 48. Hallux Valgus

Metatarsal Fracture

- as with the hand, 1st, 4th, 5th metatarsals (MT) are relatively mobile, while the 2nd and 3rd are fixed (Table 18)
- use Ottawa Foot Rules to determine need for x-ray (see sidebar)

Table 18. Types of Metatarsal Fractures

Fracture Type	Mechanism	Clinical	Treatment
Avulsion of base of 5th MT	Sudden inversion followed by contraction of peroneus brevis	Tender base of 5th MT	Requires ORIF if displaced
Midshaft 5th MT (Jones fracture)	Stress injury	Painful shaft of 5th MT	*NWB BK cast x 6 wks ORIF if athlete
Shaft 2nd, 3rd MT (March fracture)	Stress injury	Painful shaft of 2nd or 3rd MT	Symptomatic
1st MT	Trauma	Painful 1st MT	ORIF if displaced otherwise NWB BK cast x 3 wks then walking cast x 2 wks
Tarso-MT fracture – dislocation	Fall onto plantar flexed foot or direct crush injury	Shortened forefoot prominent base	ORIF (Lisfranc fracture)

* NWB BK = Non weight bearing, below knee cast



Ottawa Foot Rules

X-rays only required if:
Pain in the midfoot zone AND bony tenderness over the navicular or base of the fifth metatarsal OR inability to weight bear both immediately after injury and in the ER.

Pediatric Orthopaedics

Fractures in Children



Greenstick fractures are easy to reduce but can redisplace while in cast due to intact periosteum.

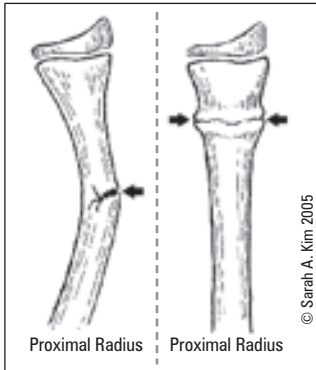


Figure 49. Greenstick (left) and Torus (right) Fractures

- type of fracture
 - usually greenstick or buckle because periosteum is thicker and stronger
 - adults fracture through both cortices
- epiphyseal growth plate
 - plate often mistaken for fracture and vice versa
 - x-ray opposite limb for comparison
 - mechanism which causes ligamentous injury in adults causes growth plate injury in children
 - intra-articular fractures have worse consequences in children because they usually involve the growth plate
- anatomic reduction
 - gold standard with adults
 - may cause limb length discrepancy in children (overgrowth)
 - accept greater angular deformity in children (remodeling minimizes deformity)
- time to heal
 - shorter in children
- always be aware of the possibility of child abuse
 - make sure mechanism compatible with injury
 - high index of suspicion, look for other signs, including x-ray evidence of healing fractures at other sites

Stress Fractures

Mechanism

- insufficiency fracture
 - stress applied to a weak or structurally deficient bone
- fatigue fracture
 - repetitive, excessive force applied to normal bone
- most common in adolescent athletes
- tibia is most common site

Diagnosis and Treatment

- localized pain and tenderness over the involved bone
- plain films may not show fracture for 2 weeks
- bone scan +ve in 12-15 days
- treatment is rest from strenuous activities to allow remodeling (can take several months)

Evaluation of the Limping Child

- see Pediatrics, P95

Epiphyseal Injury

Table 19. Salter-Harris Classification of Epiphyseal Injury

SALT(E)R-Harris Type	Description	Treatment
I (Straight through; Stable)	Transverse through growth plate	Closed reduction and cast immobilization heals well, 95% do not affect growth
II (Above)	Through metaphysis and along growth plate	
III (Low)	Through epiphysis to plate and along growth plate	Anatomic reduction by ORIF to prevent growth arrest
IV (Through and through)	Through epiphysis and metaphysis	
V (Ram)	Crush injury of growth plate	High incidence of growth arrest; no specific treatment

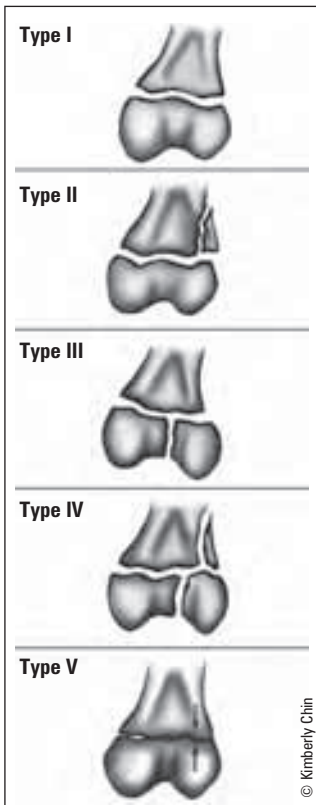


Figure 50. Salter-Harris Classification

Slipped Capital Femoral Epiphysis (SCFE)

- type I Salter-Harris epiphyseal injury
- most common adolescent hip disorder, peak at pubertal growth spurt
- risk factors: male, obese, hypothyroid

Etiology

- multifactorial
 - genetic: autosomal dominant, blacks > caucasians
 - cartilaginous physis thickens rapidly under growth hormone (GH) effects
 - sex hormone secretion, which stabilizes physis, has not yet begun
 - overweight: mechanical stress
 - trauma: causes acute slip

Clinical Features

- acute: sudden, severe pain with limp
- chronic: limp with medial knee or anterior thigh pain
- tender over joint capsule
- restricted internal rotation, abduction, flexion
 - Whitman's sign: with flexion there is an obligate external rotation of the hip
- pain at extremes of ROM

Investigations

- x-rays: AP, frog-leg, lateral radiographs
 - posterior and medial slip
 - if mild slip, AP view may be normal or show slightly widened growth plate compared with opposite side

Treatment and Complications

- mild/moderate slip: stabilize physis with pins in current position
- severe slip: ORIF or pin physis without reduction and osteotomy after epiphyseal fusion
- complications: AVN (most common), chondrolysis, pin penetration, premature OA, loss of ROM



In slipped capital femoral epiphysis, bilateral involvement occurs in about 25%.

Developmental Dysplasia of the Hip (DDH)

- formerly called congenital dysplasia of the hip (CDH)
- due to ligamentous laxity, muscular underdevelopment, and abnormal shallow slope of acetabular roof
- spectrum of conditions that lead to hip subluxation and dislocation
 - dislocated femoral head completely out of acetabulum
 - dislocatable head in socket
 - head subluxates out of joint when provoked
 - dysplastic acetabulum, more shallow and more vertical than normal
- painless (if painful suspect septic dislocation)

Physical Examination

- diagnosis is clinical
 - limited abduction of the flexed hip (<50-60°)
 - affected leg shortening results in asymmetry in skin folds and gluteal muscles, wide perineum
 - Barlow's test (for dislocatable hip)
 - ♦ flex hips and knees to 90° and grasp thigh
 - ♦ fully adduct hips, push posteriorly to try to dislocate hips
 - Ortolani's test (for dislocated hip)
 - ♦ initial position as above but try to reduce hip with fingertips during abduction
 - ♦ positive test: palpable clunk is felt (not heard) if hip is reduced
 - Galeazzi's Sign
 - ♦ knees at unequal heights when hips and knees flexed
 - ♦ dislocated hip on side of lower knee
 - ♦ difficult test if child <1 year
 - false positive if congenital short femur
 - ♦ Trendelenburg test and gait useful if older (>2 years)



5 F's that Predispose to Developmental Dysplasia of the Hip
 Family history
 Female
 Frank breech
 First born
 LeFt hip

Investigations

- U/S in first few months to view cartilage
- follow up radiograph after 3 months

Treatment and Complications

- 0-6 months: reduce hip using Pavlik harness to maintain abduction and flexion
- 6-18 months: reduction under GA, hip spica cast x 2-3 months (if Pavlik harness fails)
- >18 months: open reduction; pelvic and/or femoral osteotomy
- complications
 - redislocation, inadequate reduction, stiffness
 - AVN of femoral head

Legg-Calve-Perthes Disease (Coxa Plana)

- self-limited AVN of femoral head, presents at 4-10 years of age
- etiology unknown, 20% bilateral, males > females, 1/10,000
- associations
 - family history
 - low birth weight
 - abnormal pregnancy/delivery
 - history of trauma to affected hip
- key features
 - AVN of proximal femoral epiphysis, abnormal growth of the physis, and eventual remodelling of regenerated bone

Clinical Features

- child with hip pain and limp
- tender over anterior thigh
- flexion contracture: decreased internal rotation, abduction of hip

Investigations

- x-rays
 - may be negative early
 - eventually, characteristic collapse of femoral head (diagnostic)
- subchondral fracture
- metaphyseal cyst

Treatment

- goal is to preserve ROM and preserve femoral head in acetabulum
- PT: ROM exercises
- brace in flexion and abduction x 2-3 years
- femoral or pelvic osteotomy
- prognosis better in
 - males <5 years old, <50% of femoral head involved, abduction >30°
- 50% of involved hips do well with conservative treatment
- complicated by early onset osteoarthritis and decreased ROM

Osgood-Schlatter Disease**Mechanism**

- repetitive tensile stress on insertion of patellar tendon over the tibial tuberosity causes minor avulsion at the site and subsequent inflammatory reaction (tibial tubercle apophysitis)
- most common in adolescent athletes, especially jumping sports

Clinical Features

- tender lump over tibial tuberosity
- pain on resisted leg extension
- anterior knee pain exacerbated by jumping or kneeling, relieved by rest

Investigations

- x-rays: fragmentation of the tibial tubercle, ± ossicles in patellar tendon

Treatment

- benign, self-limited condition
- may restrict activities such as basketball or cycling
- flexibility, strengthening exercises

Congenital Talipes Equinovarus (Club Foot)

- fixed deformity
- 3 parts to deformity
 - talipes: talus is inverted and internally rotated
 - equinus: ankle is plantar flexed
 - varus: heel and forefoot are in varus (supinated)
- may be idiopathic, neurogenic, or syndrome-associated
- 1-2/1,000 newborns, 50% bilateral, occurrence M>F, severity F>M

Physical Examination

- examine hips for associated DDH
- examine knees for deformity
- examine back for dysraphism (unfused vertebral bodies)

Treatment

- correct deformities in the following order (Ponseti Technique):
 - forefoot adduction, ankle inversion, equinus
 - ♦ change strapping/cast q1-2 weeks
 - surgical release in refractory case (50%)
 - ♦ delayed until 3-4 months of age
- 3 year recurrence rate = 5-10%
- mild recurrence common; affected foot is permanently smaller/stiffer than normal foot with calf muscle atrophy

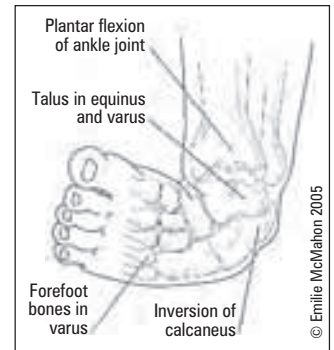


Figure 51. The Club Foot – Depicting the Gross and Bony Deformity

Scoliosis

Definition

- lateral curvature of spine with vertebral rotation

Epidemiology

- age: 10-14 years
- more frequent and more severe in females

Etiology

- idiopathic: most common (90%)
- congenital: vertebrae fail to form or segment
- neuromuscular: UMN or LMN lesion, myopathy
- other: osteochondrodystrophies, neoplastic, traumatic
- postural: leg length discrepancy, muscle spasm

Clinical Features

- \pm back pain
- 1° curve where several vertebrae affected
- 2° curves above and below fixed 1° curve to try and maintain normal position of head and pelvis
- asymmetric shoulder height when bent forward
- Adam's test: rib hump when bent forward
- prominent scapulae, creased flank, asymmetric pelvis
- associated posterior midline skin lesions in non-idiopathic scolioses
 - café-au-lait spots, dimples, neurofibromas
 - axillary freckling, hemangiomas, hair patches
- associated pes cavus or leg atrophy
- apparent leg length discrepancy

X-Rays

- 3-foot standing
 - measure curvature – Cobb Angle (Figure 52)
 - may have associated kyphosis

Treatment

- based on degree of curvature
 - <20°: observe for changes
 - >20° or progressive: bracing (many types) that halt/slow curve progression but do NOT reverse deformity
 - >40°, cosmetically unacceptable or respiratory problems: surgical correction (spinal fusion)

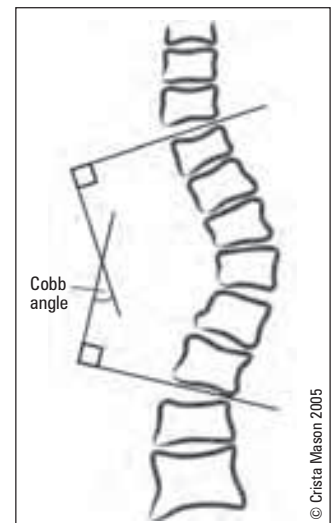


Figure 52. Cobb Angle – used to monitor the progression of the scoliotic curve



In structural or fixed scoliosis, bending forwards makes the curve more obvious.



Postural scoliosis can be corrected by correcting the underlying problem.

Bone Tumours



Red Flags

- Persistent skeletal pain
- Localized tenderness
- Spontaneous fracture
- Enlarging mass/soft tissue swelling

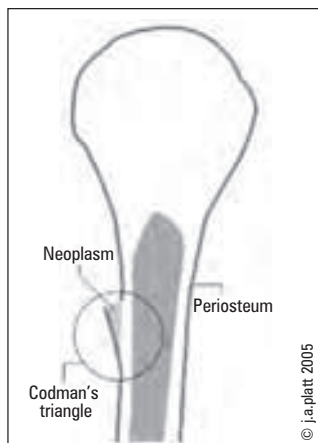


Figure 53. Codman's Triangle – a radiographic finding in malignancy, where the partially ossified periosteum is lifted off the cortex by neoplastic tissue



Figure 54. T1 MRI of Femoral Enchondroma

- primary bone tumours are rare after 3rd decade
- metastases to bone are relatively common after 3rd decade

Diagnosis

- pain, swelling, tenderness, rarely regional adenopathy
- routine x-ray
 - location (which bone, diaphysis, metaphysis, epiphysis)
 - size
 - lytic/lucent vs. sclerotic
 - involvement (cortex, medulla, soft tissue)
 - matrix (radiolucent, radiodense or calcified)
 - periosteal reaction
 - margin (geographic vs. permeative)
 - any pathological fracture
 - soft tissue swelling
- malignancy is suggested by rapid growth, warmth, tenderness, lack of sharp definition
- staging should include
 - bloodwork including liver enzymes
 - CT chest
 - bone scan
 - bone biopsy
 - ♦ should be referred to specialized centre prior to biopsy
 - ♦ classified into benign, benign aggressive, and malignant
 - MRI of affected bone

Benign Active Bone Tumours

1. Osteoid Osteoma

- peak incidence in 2nd and 3rd decades, M:F = 3:1
- small, round radiolucent nidus (<1 cm) surrounded by dense bone
 - tibia and femur most common
- produces severe intermittent pain, mostly at night (diurnal prostaglandin production)
- characteristically relieved by NSAIDs
- not known to metastasize

2. Osteochondroma

- 2nd and 3rd decades, M:F = 1.8:1
- 45% of all benign bone tumours
- metaphysis of long bone (distal ends of femur/proximal ends of humerus)
 - cartilage-capped bony spur on surface of bone ("mushroom" on x-ray)
 - may be multiple (hereditary, autosomal dominant form) – higher risk of malignant change
- generally very slow growing and asymptomatic unless impinging on neurovascular structure
- malignant degeneration occurs in 1-2% (becomes painful or rapidly grows)

3. Enchondroma (Figure 54)

- 2nd and 3rd decades
- 50% occur in the small tubular bones of the hand and foot; others in femur, humerus, ribs
- benign cartilagenous growth, develops in medullary cavity
 - single/multiple enlarged rarefied areas in tubular bones
 - lytic lesion with sharp margination and central calcification
- malignant degeneration occurs in 1-2% (pain in absence of pathologic fracture is an important clue)
- not known to metastasize

4. Cystic Lesions

- includes unicameral/solitary bone cyst (most common), fibrous cortical defect
- children and young adults
- local pain, pathological fracture (50% presentations) or incidental detection
 - lytic translucent area on metaphyseal side of growth plate
 - cortex thinned/expanded; well defined lesion
- aspiration cystic fluid: green/yellow colour with high ALP
- treatment of unicameral bone cyst with steroid injections ± bone graft

Treatment

- treatment only necessary if symptomatic
- osteochondroma: resection
- cystic lesions: curettage and bone graft

Benign Aggressive Bone Tumours

Giant Cell Tumours/Aneurysmal Bone Cyst/Osteoblastoma (Figure 55)

- affects patients of skeletal maturity, peak 3rd decade
- found in the distal femur, proximal tibia, distal radius, sacrum, tarsal bones, spinal (osteoblastoma)
- cortex appears thinned, expanded; well-demarcated sclerotic margin; T2 MRI enhances fluid within lesion (hyper-intense signal)
- local tenderness and swelling
- 15% recur within 2 years of surgery
- giant cell tumour occasionally metastasizes (1-2%)

Treatment

- intralesional curettage + bone graft or cement
- wide local excision of expendable bones

Malignant Bone Tumours

Table 20. Most Common Malignant Tumour Types for Age

Age	Tumour
<1	Neuroblastoma
1-10	Ewing's of tubular bones
10-30	Osteosarcoma, Ewing's of flat bones
30-40	Reticulum cell sarcoma, fibrosarcoma, periosteal osteosarcoma, malignant giant cell tumour, lymphoma
>40	Metastatic carcinoma, multiple myeloma, chondrosarcoma

1. Osteosarcoma (Figure 56)

- most frequently diagnosed in 2nd decade of life (60%)
- history of Paget's disease radiation
- predilection for distal femur (45%), proximal tibia (20%) and proximal humerus (15%)
 - invasive, variable histology; frequent metastases without treatment (lung most common)
- painful, poorly defined swelling, decreased ROM
- x-ray shows Codman's triangle (Figure 53)
 - characteristic periosteal elevation and spicule formation representing tumour extension into periosteum
 - destructive lesion in metaphysis may cross epiphyseal plate
- treatment: complete resection (limb salvage, rarely amputation), neo-adjuvant chemo
- survival – 70%

2. Chondrosarcoma (Figure 57)

- primary (2/3 cases)
 - previous normal bone, patient over 40; expands into cortex to give pain, pathological fracture, flecks of calcification
- secondary (1/3 cases)
 - malignant degeneration of pre-existing cartilage tumour such as enchondroma or osteochondroma, younger age group and better prognosis than primary chondrosarcoma
- most commonly occurs in pelvis, femur, ribs, scapula, humerus (with metastasis to the lung)
- unresponsive to chemotherapy, treat with aggressive surgical resection + reconstruction

3. Ewing's Sarcoma

- most occur between 5-20 years old
- florid periosteal reaction in diaphysis of long bone
 - moth-eaten appearance with periosteal lamellated pattern (onion-skinning)
- present with mild fever, anemia, leukocytosis and increased ESR/LDH
- metastases frequent without treatment
- treatment – resection, chemotherapy, radiation
- survival – 70%

4. Multiple Myeloma

- most common primary malignant tumour of bone in adults
- 90% occur in people >40 years old
- present with anemia, anorexia, renal failure, nephritis, increased ESR, bone pain (cardinal early symptom), compression fractures, hypercalcemia
- high incidence of infections (e.g. pyelonephritis/pneumonia)



Figure 55. X-Ray of Aneurysmal Bone Cyst. Note the aggressive destruction of bone



Figure 56. X-Ray of Osteosarcoma of Distal Femur

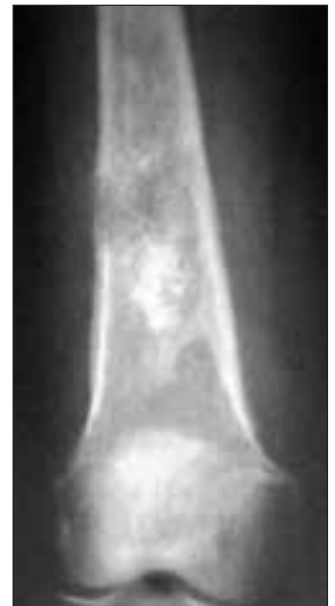
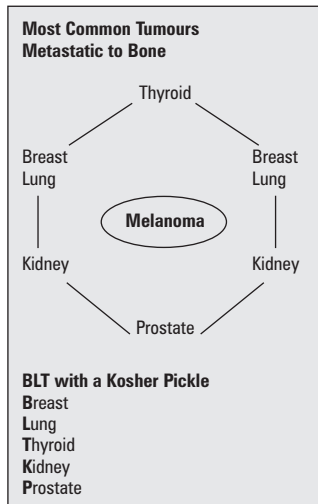


Figure 57. X-Ray of Femoral Chondrosarcoma



- diagnosis
 - CT-guided biopsy of lytic lesions at multiple bony sites
 - serum/urine protein electrophoresis
- treatment: chemotherapy, radiation, surgery for symptomatic lesions or impending fractures
- see [Hematology](#), H47

5. Bone Metastases

- 2/3 from breast or prostate; also consider thyroid, lung, kidney
- usually osteolytic; prostate occasionally osteoblastic
- bone scan for MSK involvement, MRI for spinal involvement may be helpful
- stabilization of impending fractures
 - internal fixation, IM rods
 - bone cement

Articular Cartilage Defects

Properties of Articular Cartilage

- lacks blood supply and does not have innervation or lymphatic drainage
- varies in thickness from 2 mm to 4 mm and is thickest at periphery of concave surfaces and central portions of convex surfaces
- composed of type 2 collagen, water, proteoglycans, and chondrocytes
- collagen provides resistance against tensile stresses and transmits vertical loads
- water and proteoglycans provide turgor and elasticity and help to limit friction
- chondrocytes synthesize the cartilage matrix and control matrix turnover rate

Etiology

- overt trauma or repeated minor trauma; most commonly from sports injuries
- early stage osteoarthritis
- genetic degenerative diseases such as osteochondritis dissecans

Clinical Features

- very similar to symptoms of osteoarthritis (joint line pain with possible effusion, etc.)
- often have predisposing factors such as ligament injury, malalignment of the joint (varus/valgus), obesity, bone deficiency (avascular necrosis, osteochondritis dissecans, ganglion bone cysts), inflammatory arthropathy, and familial osteoarthopathy
- may have symptoms of locking or catching related to the torn/displaced cartilage

Investigations

- arthroscopy to visualize focal pathology and guide treatment strategy
- MRI may also be used to visualize the defect

Table 21. Outerbridge Classification of Chondral Defects

Grade	Chondral Damage
I	Softening and swelling of cartilage
II	Fragmentation and fissuring < 1/2 inch in diameter
III	Fragmentation and fissuring > 1/2 inch in diameter
IV	Erosion of cartilage down to bone

Treatment

- arthroscopic lavage and debridement of the joint
- marrow stimulation techniques (microfracture, drilling, abrasion arthroplasty)
 - involves creating a site of bleeding where new growth/healing can take place
- osteochondral grafts; also known as the OATS procedure or mosaicplasty
 - involves transferring osteochondral fragments from non-weightbearing surface to area of defect
- autologous chondrocyte implantation (ACI)
 - currently only available in the U.S. and Europe
 - involves harvesting patient's cartilage, growing it in culture medium outside of the patient, then reinserting the newly cultured chondrocytes back to fill the chondral defect
- osteochondral allograft; only used in limited circumstances when defect is very large

Common Medications

Table 22. Common Medications

Drug Name	Dosing Schedule	Indications	Comments
cefazolin (Ancef®)	1-2 g IV q8h	Prophylactically before orthopaedic surgery	First generation cephalosporin; do not use with penicillin allergy
heparin	5000 IU SC q12h	To prevent venous thrombosis and pulmonary emboli	Monitor platelets, follow PTT which should rise 1.5-2x
LMWH dalteparin (Fragmin®) enoxaparin (Lovenox®) fondaparinux (Arixtra®)	5000 IU SC OD 30-40 mg SC bid 2.5 mg SC OD	DVT prophylaxis esp. in hip and knee surgery	Fixed dose, no monitoring, improved bioavailability, increased bleeding rates
midazolam (Versed®)	0.02 mg/kg IV	Conscious sedation for short procedures	Medications used together during fracture reduction – monitor for respiratory depression
fentanyl (Sublimaze®)	0.5-3 µg/kg IV	Conscious sedation for short procedures	Short acting anesthetic used in conjunction with midazolam (Versed®)
triamcinolone (Aristocort®) – an injectable steroid	0.5-1 mL of 25 mg/mL	Suspension (injected into inflamed joint or bursa)	Potent anti-inflammatory effect Increased pain for 24 hours, rarely causes fat necrosis and skin depigmentation
naproxen (Naprosyn®)	250-500 mg bid	Pain due to inflammation, arthritis, soft tissue injury	NSAID, may cause gastric erosion and bleeding
misoprostol (Cytotec®)	200 µg qid	Prophylaxis of heterotopic ossification after THA	Use with indomethacin
indomethacin (Indocid®)	25 mg PO tid	Prophylaxis of heterotopic ossification after THA	Use with misoprostol
ibuprofen (Advil®, Motrin®)	200-400 mg tid	Pain (including post-op), inflammation (including arthritis)	NSAID, may cause gastric erosion and bleeding
propofol (Diprivan®)	1-2 mg/kg IV Maint 0.5 mg/kg	Conscious sedation for short procedures	Short acting anesthetic often used in conjunction with fentanyl (Sublimaze®)

References

Textbooks

- Adams JC, Hamblen DL. Outline of fractures: including joint injuries. 11th ed. Toronto (ON): Churchill Livingstone, 1999.
- Blackbourne LH. Surgical recall. 3rd ed. LH Blackbourne. Philadelphia (PA): Lippincott Williams & Wilkins, 2002.
- Brinker MR. Review of orthopaedic trauma. Toronto (ON): W.B. Saunders Company, 2001.
- Brinker M, Miller M. Fundamentals of orthopaedics. Philadelphia (PA): W.B. Saunders, 1999.
- Dee R, Hurst LC, Gruber MA, Kottmeier SA, editors. Principles of orthopaedic practice. 2nd Toronto (ON): McGraw-Hill, 1997.
- Kao LD. Pre-test surgery. Toronto (ON): McGraw-Hill, 2002.
- Ochiai DH. The orthopaedic intern pocket survival guide. McLean (VA): International Medical Publishing, 2007.
- Rockwood CA Jr, Greene DP, Bucholz RU, Heckman JD, editors. Rockwood and Green's fractures in adults. 4th ed. Philadelphia (PA): Lippincott Raven, 1996.
- Skinner HB. Current diagnosis and treatment in orthopaedics. 4th ed. New York (NY): McGraw-Hill, 2006.
- Solomon L, Warwick DJ, Nayagam, S. Apley's system of orthopaedics and fractures. 8th ed. New York (NY): Hodder Arnold, 2001.
- Thompson JC. Netter's concise atlas of orthopaedic Anatomy. [USA]: Elsevier, 2001.

Journal Articles

- Adkins SB. Hip pain in athletes. Am Fam Physician. 2000;61(7):2109-2118.
- Armagan OE, Shreff MJ. Injuries of the toes and metatarsals. Orthop Clin North Am. 2001;32(1):1-10.
- Barei DP, Bellabarba C, Sangeorzan BJ, Benirschke SK. Fractures of the calcaneus. Orthop Clin North Am. 2001;33(1):263-285.
- Barrett SL. Plantar fasciitis and other causes of heel pain. Am Fam Physician. 1999;59(8):2200-2206.
- Brand DA, Frazier WH, Kohlhepp WC, et al. A protocol for selecting patients with injured extremities who need x-rays. NEJM. 1982;306:833-339.
- Canadian CT Head and C-Spine (CCC) Study Group. Canadian c-spine rule study for alert and stable trauma patients: 1. Background and rationale. CJEM. 2002; 4(2): 84-90.
- Carek PJ. Diagnosis and management of osteomyelitis. Am Fam Physician. 2001;63(12): 2413-2420.
- Donatto KC. Ankle fractures and syndesmosis injuries. Orthop Clin North Am. 2001;32(1):79-90.
- Fernandez M. Discitis and vertebral osteomyelitis in children: an 18-year review. Pediatrics. 105(6): 1299-1304.
- Fortin PT. Talus fractures: evaluation and treatment. J Am Acad Orthop Surg. 2001;9(2): 114-127.
- French B, Tornetta III P. High energy tibial shaft fractures. Orthop Clin North Am. 2002;33(1):211-230.
- Gable, H Nunn, D. Image Interpretation Course. 2009 <http://www.imageinterpretation.co.uk>; accessed May 18, 2010
- Gustilo RB, Mendoza RM, Williams DN. Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. J Trauma. 1984;24:742-746.
- Geerts WH, Heit JA, Clagett, GP et al. Prevention of venous thromboembolism. Chest. 2001;119(1 Suppl): 132S-175S.
- Harty MP. Imaging of pediatric foot disorders. Radiol Clin North Am. 2001;39(4):733-748.
- Irrgang JJ. Rehabilitation of multiple ligament injured knee. Clin Sports Med. 2000;19(3): 545-571.
- Lawrence LL. The limping child. Emerg Med Clin North Am. 1998;169(4):911-929.
- Lo, I.K. NB, Woolfrey, M., Litchfield, R., & Kirkey, A. An evaluation of the apprehension, relocation, and surprise tests for anterior shoulder instability. American Journal of Sports Medicine, 2004;32, 301-307.
- Luime JJ, Verhagen AP, Miedema HS, Kuiper JJ, Burdorf A, Verhaar JAN, Koes BW. An Evaluation of the Apprehension, Relocation, and Surprise Tests for Anterior Shoulder Instability. The American Journal of Sports Medicine. 2004;32:301-307.
- Mazzone MF. Common conditions of the Achilles tendon. Am Fam Physician. 2000;65(9):1805-1810.
- Steele PM, Bush-Joseph C, Bach Jr B. Management of acute fractures around the knee, ankle, and foot. Clin Fam Pract. 2000;2(3):661-705.
- Miller SL. Malignant and benign bone tumours. Radiol Clin North Am. 2000;39(4): 673-699.
- Oudjhane K. Imaging of osteomyelitis in children. Radiol Clin North Am. 2001;39(2): 251-266.
- Patel DR. Sports injuries in adolescents. Med Clin North Am. 2000;84(4):983-1007.
- Roberts DM, Stallard TC. Emergency department evaluation and treatment of knee and leg injuries. Emerg Med Clin North Am. 2000;18(1):67-84.
- Russell GV Jr. Complicated femoral shaft fractures. Orthop Clin North Am. 2002;33(1): 127-142.
- Solomon DH, Simel DL, Bates DW, Katz JN, Schaffer JL. The rational clinical examination. Does this patient have a torn meniscus or ligament of the knee? Value of the physical examination. JAMA. 2001;286(13):1610-20.
- St Pierre P. Posterior cruciate ligament injuries. Clin Sports Med. 1999;18(1): 199-221.
- Steele PM, Bush-Joseph C, Bach Jr B. Management of acute fractures around the knee, ankle, and foot. Clin Fam Pract. 2000;2(3):661-705.
- Stewart DG, Kay RM, Skaggs DL. Open fractures in children. Principles of evaluation and management. JBJS Am. 2005;87: 2784-2798.
- Swenson TM. The dislocated knee: physical diagnosis of the multiple-ligament-injured knee. Clin Sports Med. 2000;19(3):415-423.
- Zollinger PE, Tuinebreijer WE, Kreis RW, Breederveld RS. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomized trial. Lancet. 1999;354(9195): 2025-2028.

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Basic Anatomy Review

Ear

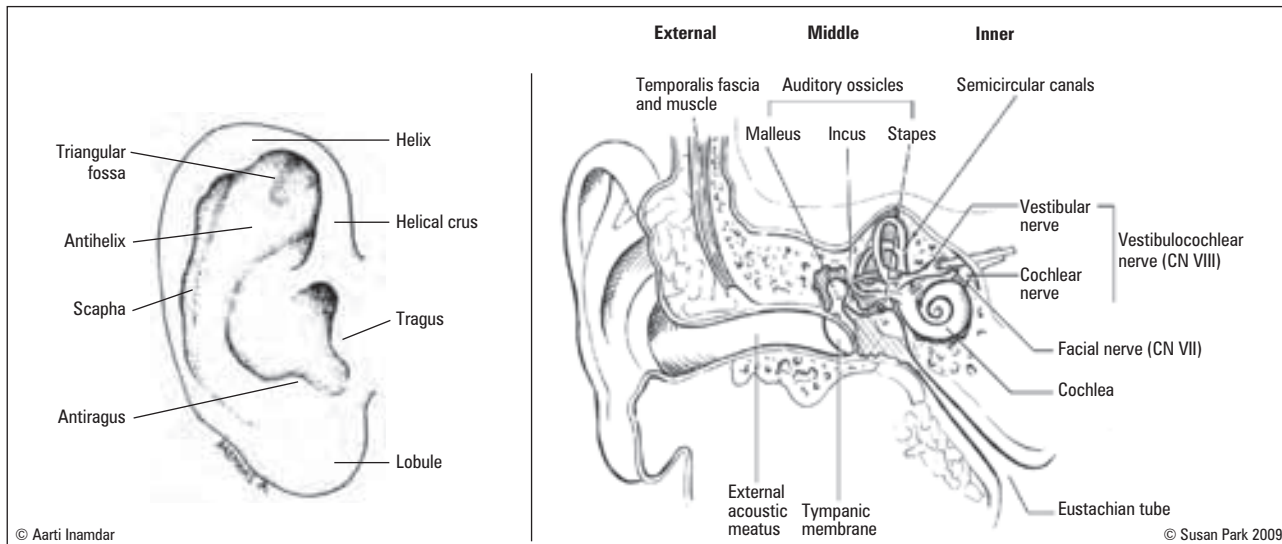


Figure 1. Surface Anatomy of the External Ear; Anatomy of Ear

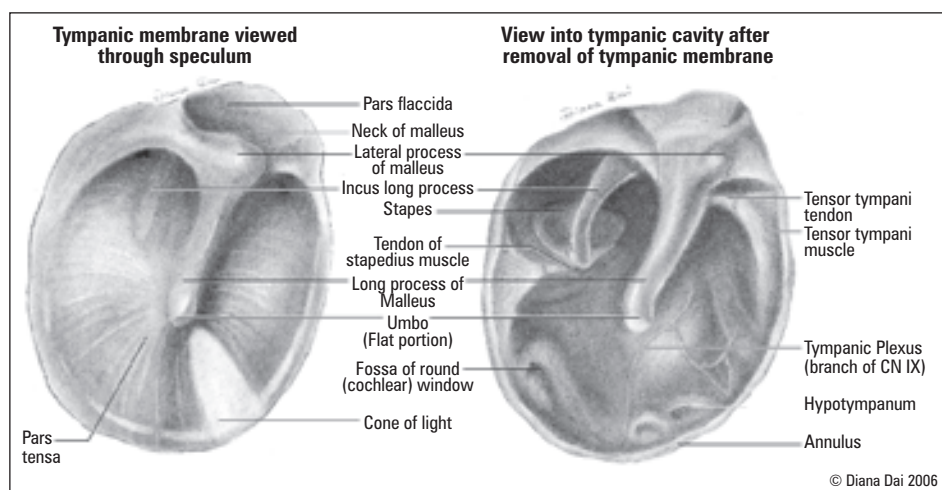


Figure 2. Normal Appearance of Right Tympanic Membrane on Otoscopy

Nose



Drainage into Nasal Cavity

Superior meatus: sphenoid (via sphenodethmoidal recess), posterior ethmoid sinuses

Middle meatus: frontal, maxillary, anterior ethmoid sinuses

Inferior meatus: nasolacrimal duct

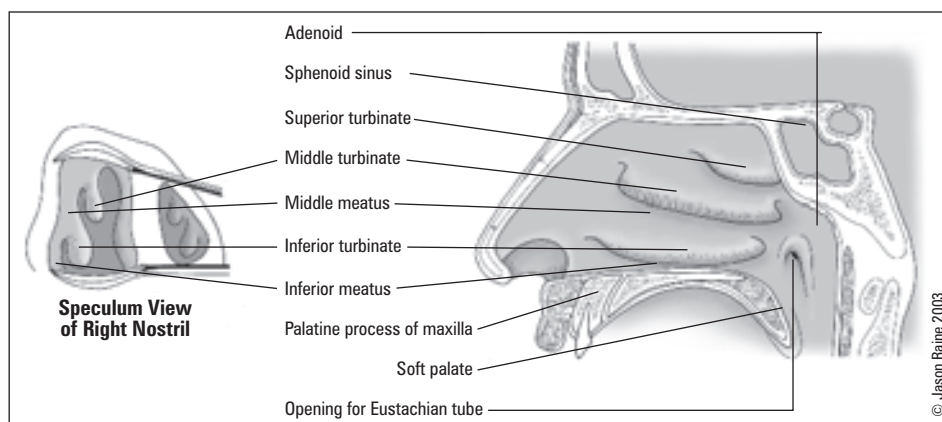


Figure 3. Nasal Anatomy

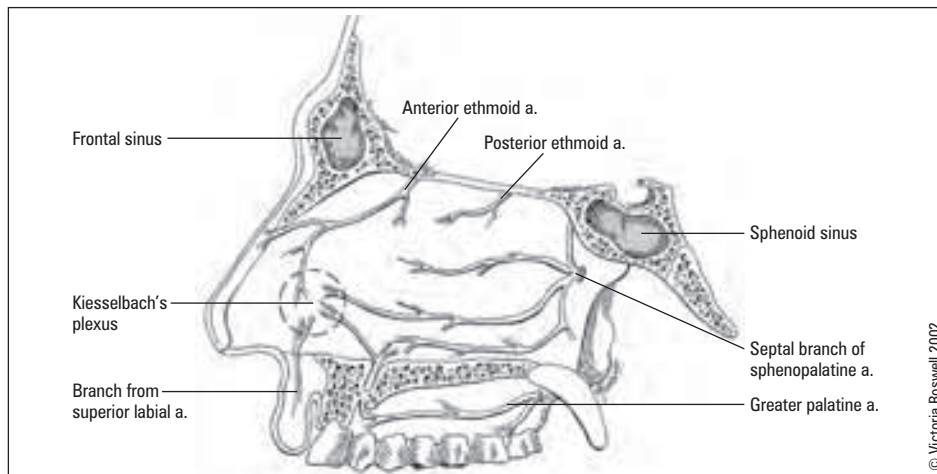


Figure 4. Nasal Septum and its Arterial Supply (see Epistaxis section for detailed blood supply)

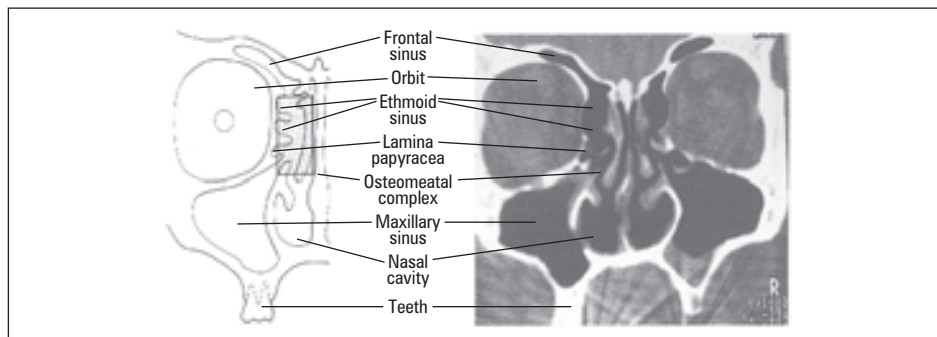


Figure 5. Anatomy of the Four Paranasal Sinuses: Maxillary, Ethmoid, Sphenoid, and Frontal

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Nasopharynx: skull base to soft palate
Oropharynx: soft palate to hyoid bone
Laryngopharynx: hyoid bone to inferior cricoid cartilage

Throat

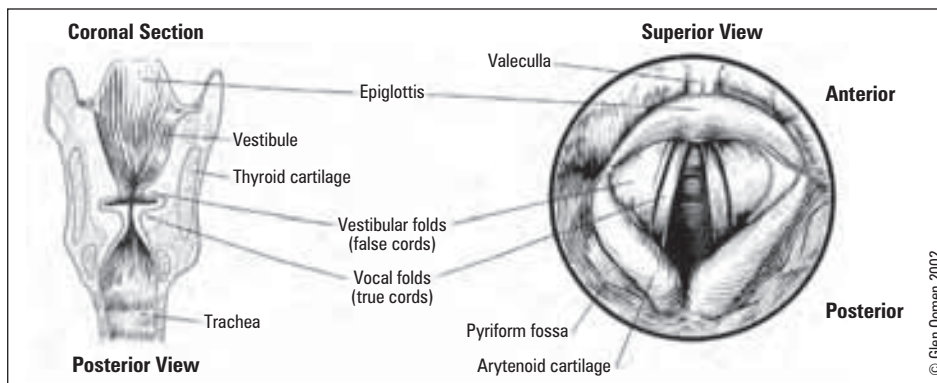


Figure 6. Anatomy of a Normal Larynx; Superior View of Larynx on Indirect Laryngoscopy

Head and Neck

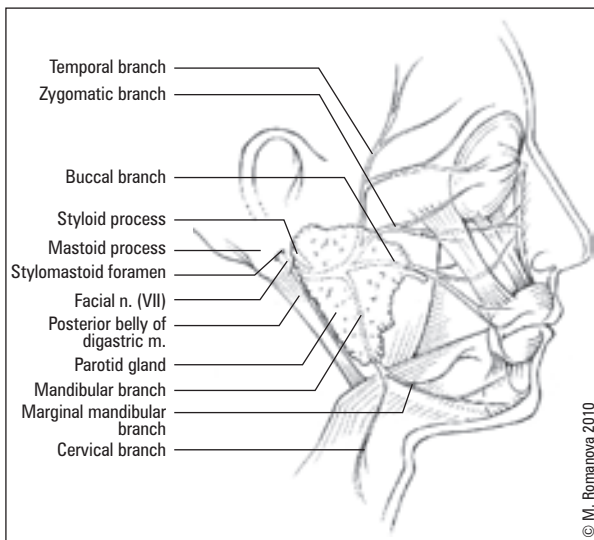


Figure 7. Extratemporal Segment of Facial Nerve
Branches of Facial Nerve (in order from superior to inferior)
 Ten Zebras Broke My Car

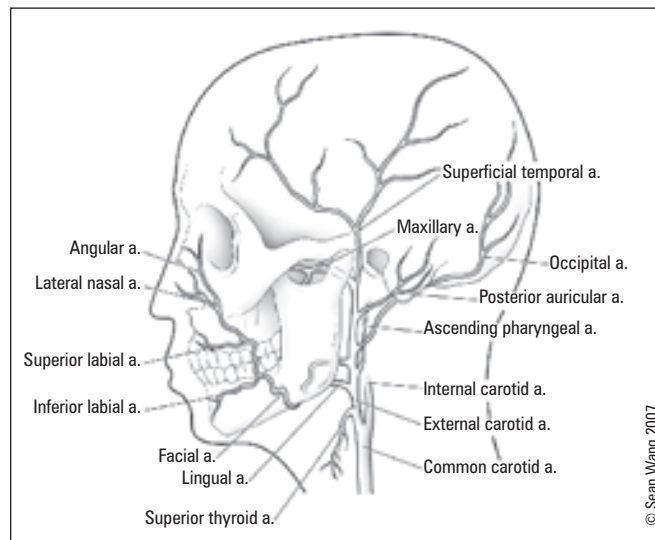


Figure 8. Blood Supply to the Face
Branches of the External Carotid Artery (in order from inferior to superior)
 Some Angry Lady Figured Out PMS

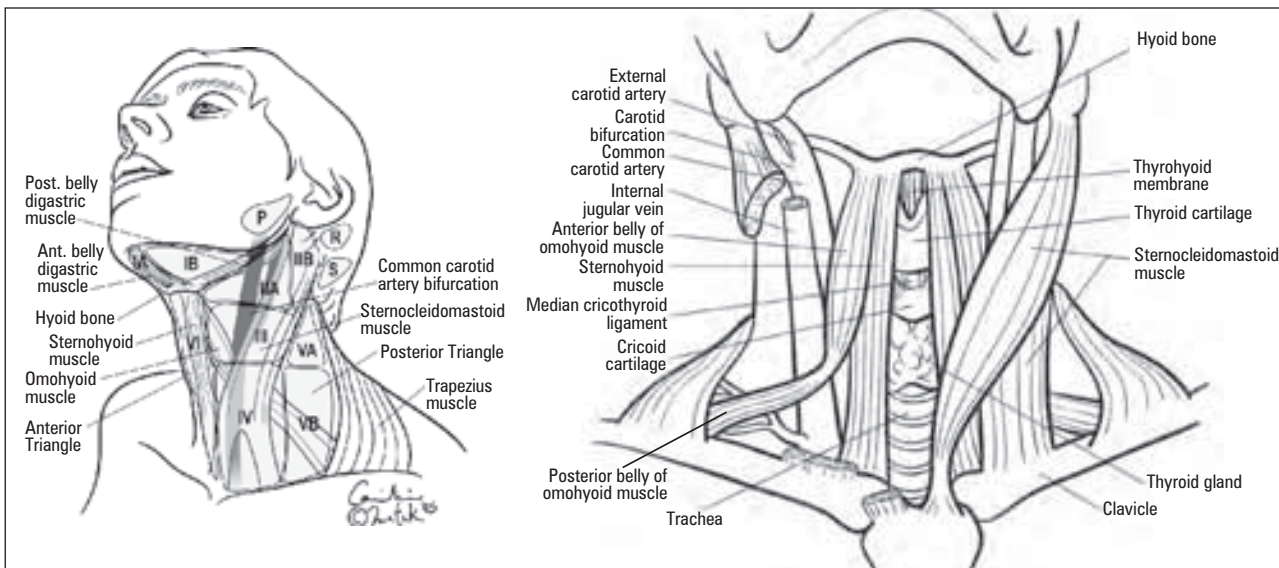


Figure 9. Anatomy of the Neck



Paired Parasympathetic Ganglia of the Head and Neck

Ciliary – pupillary constriction
Pterygopalatine – lacrimal gland, nasal mucosa
Submandibular – submandibular, sublingual glands
Otic – parotid gland



Function of Facial Nerve “Ears, Tears, Face, Taste”

Ears – stapedius muscle
Tears – lacrimation (lacrimal gland) and salivation (parotid)
Face – muscles of facial expression
Taste – sensory anterior 2/3 of tongue (via chorda tympani)

Anatomical Triangles of the Neck

- **anterior triangle:**
 - bounded by anterior border of sternocleidomastoid (SCM), midline of neck, and lower border of mandible
 - divided into:
 - ♦ **submental triangle:** bounded by both anterior bellies of digastrics and hyoid bone
 - ♦ **digastric triangle:** bounded by anterior and posterior bellies of digastric, and inferior border of mandible
 - ♦ **carotid triangle:** bounded by sternocleidomastoid, anterior belly of omohyoid, and posterior belly of digastric
 - contains: tail of parotid, submandibular gland, hypoglossal nerve, carotid bifurcation, and lymph nodes

- **posterior triangle:**

- bounded by posterior border of sternocleidomastoid, anterior border of trapezius, and middle third of clavicle
- divided into:
 - ♦ occipital triangle: superior to posterior belly of the omohyoid
 - ♦ subclavian triangle: inferior to posterior belly of omohyoid
- contains: spinal accessory nerve and lymph nodes

Table 1. Lymphatic Drainage of Nodal Groups and Anatomical Triangles of Neck

Nodal Group/Level	Location	Drainage
1. Suboccipital (S)	Base of skull, posterior	Posterior scalp
2. Retroauricular (R)	Superficial to mastoid process	Scalp, temporal region, ext. auditory meatus, post. pinna
3. Parotid-preauricular (P)	In front of ear	External auditory meatus, anterior pinna, soft tissues of frontal and temporal regions, root of nose, eyelids, palpebral conjunctiva
4. Submental (Level IA)	(Midline) Anterior bellies of digastric muscles, tip of mandible, and hyoid bone	Floor of mouth, anterior oral tongue, anterior mandibular alveolar ridge, lower lip
5. Submandibular (Level IB)	Anterior belly of digastric muscle, stylohyoid muscle, body of mandible	Oral cavity, anterior nasal cavity, soft tissues of the mid-face, submandibular gland
6. Upper jugular (Levels IIA and IIB)	Skull base to inferior border of hyoid bone along SCM muscle	Oral cavity, nasal cavity, naso/oro/hypopharynx, larynx, parotid glands
7. Middle jugular (Level III)	Inferior border of hyoid bone to inferior border of cricoid cartilage along SCM muscle	Oral cavity, naso/oro/hypopharynx, larynx
8. Lower jugular* (Level IV)	Inferior border of cricoid cartilage to clavicle along SCM muscle	Hypopharynx, thyroid, cervical esophagus, larynx
9. Posterior triangle** (Levels VA and VB)	Posterior border of SCM, anterior border of trapezius, from skull base to clavicle	Nasopharynx and oropharynx, cutaneous structures of the posterior scalp and neck
10. Anterior compartment*** (Level VI)	(Midline) Hyoid bone to suprasternal notch between the common carotid arteries	Thyroid gland, glottic and subglottic larynx, apex of piriform sinus, cervical esophagus

*Virchow node: left lower level IV supraclavicular node

**Includes some supraclavicular nodes

***Includes pretracheal, precricoid, paratracheal, and perithyroidal nodes



- **Left-sided** enlargement of a supraclavicular node (Virchow's node) may indicate an abdominal malignancy.
- **Right-sided** enlargement may indicate malignancy of the mediastinum, lungs, or esophagus.
- Occipital and/or posterior auricular node enlargement may indicate rubella.

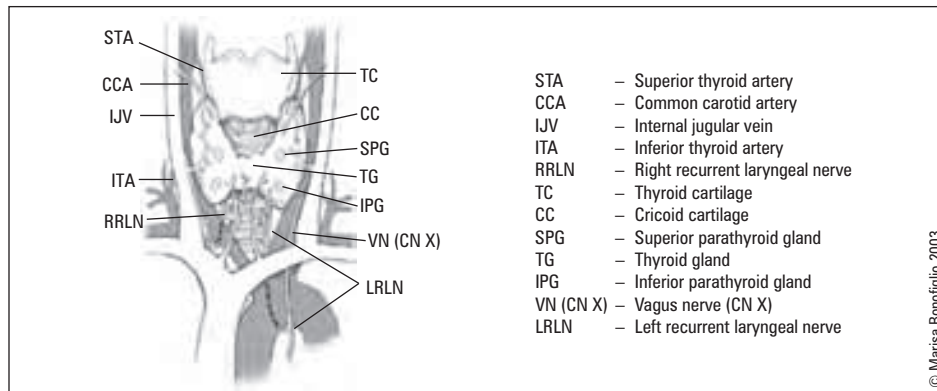
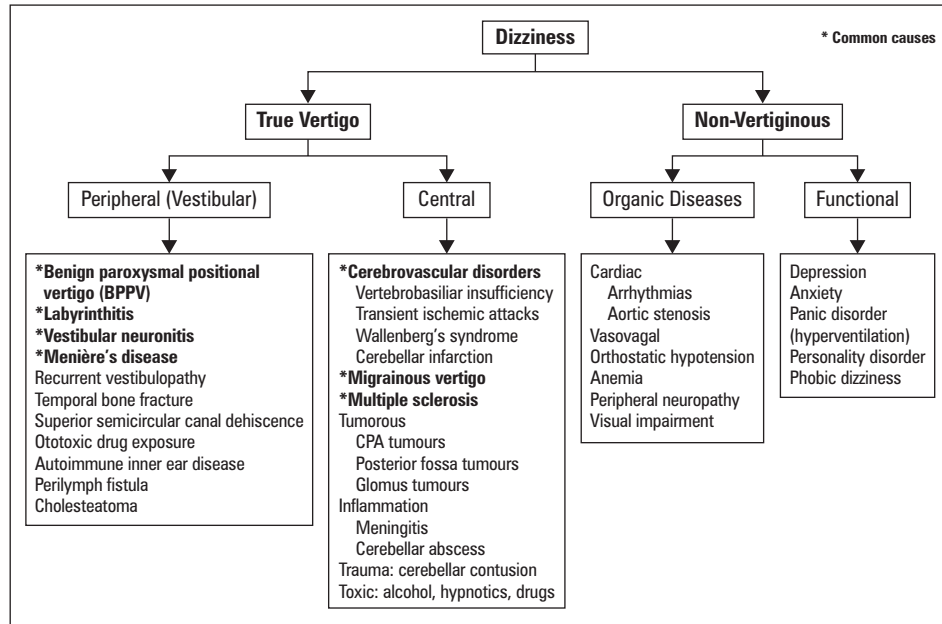


Figure 10. Anatomy of Thyroid Gland

Differential Diagnoses of Common Presenting Problems

Dizziness



True nystagmus and vertigo caused by a peripheral lesion will never last longer than a couple of weeks because of compensation. Central lesions do not compensate, hence nystagmus and vertigo will pass.



5 D's of Vertebrobasilar Insufficiency
Drop attacks
Diplopia
Dysarthria
Dizziness
Dysphagia

Figure 11. Differential Diagnosis of Dizziness



Otalgia

1. Local Causes

Table 2. Differential Diagnosis of Otalgia – Local Causes

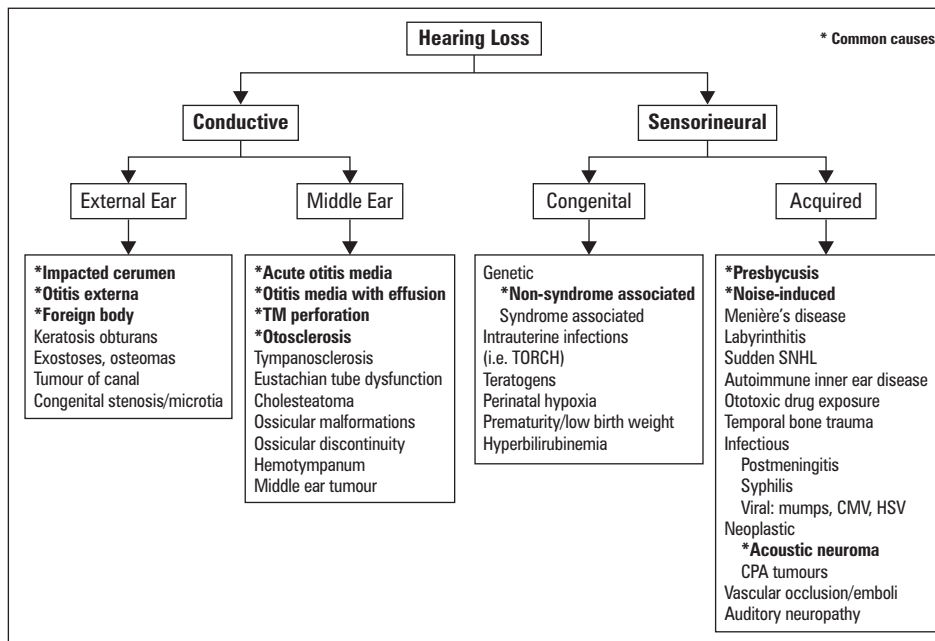
Etiology	External Ear Pain	Middle and Inner Ear Pain*
Infection	a. Otitis externa b. Herpes simplex/zoster c. Auricular cellulitis d. External canal abscess	a. Acute otitis media b. Otitis media with effusion c. Mastoiditis, myringitis, skull base infections (malignant otitis in diabetics)
Trauma	Frostbite, burns, hematoma, lacerations	Traumatic perforation, barotrauma
Other	Neoplasm of external canal, foreign body, cerumen impaction	Neoplasm, Wegener's, cholesteatoma

* primarily mediated by TM stretching

2. Referred Pain (from CN V, IX and X) – Ten T's + 2

- Eustachian Tube
- TMJ Syndrome (pain in front of the ears)
- Trismus (spasm of masticator muscles; early symptom of tetanus)
- Teeth
- Tongue
- Tonsil (tonsillitis, tonsillar cancer, post-tonsillectomy)
- Tic (glossopharyngeal neuralgia)
- Throat (cancer of larynx)
- Trachea (foreign body; tracheitis)
- Thyroiditis
- Ramsay Hunt syndrome (Geniculate Herpes)
- ± CN VII palsy (e.g. Bell's palsy)

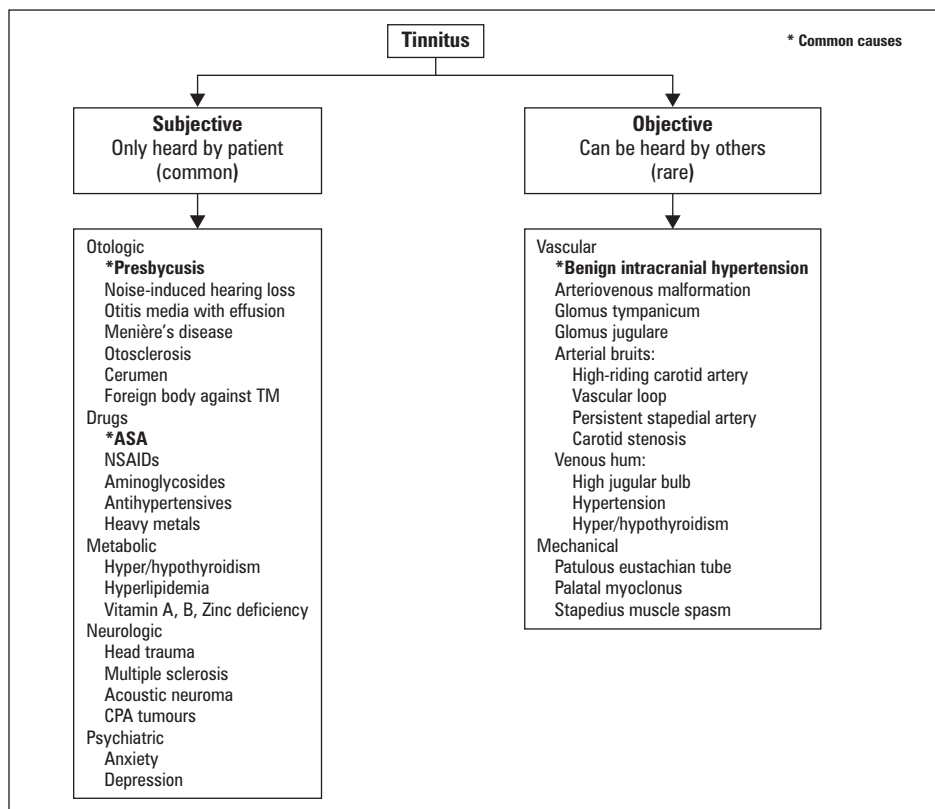
Hearing Loss



The incidence of Menière's disease has decreased since the introduction of *H. influenzae* and *S. pneumoniae* vaccines.

Figure 12. Differential Diagnosis of Hearing Loss

Tinnitus



Tinnitus is most commonly associated with SNHL.



Glomus Tympanicum/Jugulare Tumour
Signs and Symptoms

- Pulsatile tinnitus
- Hearing loss
- Blue mass behind TM
- Brown's sign (blanching of the TM with pneumatic otoscopy)

Figure 13. Differential Diagnosis of Tinnitus



Nasal Obstruction

Table 3. Differential Diagnosis of Nasal Obstruction

Acquired	Congenital
Nasal Cavity <ul style="list-style-type: none"> Rhinitis <ul style="list-style-type: none"> Acute/chronic Vasomotor Allergic Polyps Foreign bodies Enlarged turbinates Tumour <ul style="list-style-type: none"> Benign – inverting papilloma Malignant <ul style="list-style-type: none"> Squamous cell carcinoma (SCC) Esthesioneuroblastoma (olfactory neuroblastoma) Adenocarcinoma 	Nasal Cavity <ul style="list-style-type: none"> Nasal dermoid cyst Encephalocele Glioma Choanal atresia Nasal Septum <ul style="list-style-type: none"> Septal deviation Septal hematoma/abscess Dislocated septum
Nasal Septum <ul style="list-style-type: none"> Septal deviation Septal hematoma/abscess Dislocated septum 	
Nasopharynx <ul style="list-style-type: none"> Adenoid hypertrophy Tumour <ul style="list-style-type: none"> Benign – juvenile nasopharyngeal angiofibroma (JNA) Malignant – nasopharyngeal carcinoma 	
Functional <ul style="list-style-type: none"> Tunnel nose syndrome: absence of feeling in nose prevents the sensation of aeration through nostrils 	



Hoarseness

Table 4. Differential Diagnosis of Hoarseness

Infectious	<ul style="list-style-type: none"> Acute/chronic laryngitis Laryngotracheobronchitis (croup) 	
Inflammatory	<ul style="list-style-type: none"> Gastro-esophageal reflux (GERD) Vocal cord polyps/nodules Lifestyle: smoking, chronic ETOH use 	
Trauma	<ul style="list-style-type: none"> External laryngeal trauma Endoscopy and endotracheal tube (e.g. intubation granuloma) 	
Neoplasia	<ul style="list-style-type: none"> Benign tumour Papillomas (HPV infection) 	<ul style="list-style-type: none"> Malignant tumour Squamous cell carcinoma (SCC)
Cysts	<ul style="list-style-type: none"> Retention cysts 	
Systemic	<ul style="list-style-type: none"> Endocrine Hypothyroidism Virilization 	<ul style="list-style-type: none"> Connective tissue disease Rheumatoid arthritis (RA) SLE
Neurologic (vocal cord paralysis due to superior ± recurrent laryngeal nerve injury)	<ul style="list-style-type: none"> Central lesions <ul style="list-style-type: none"> Cerebrovascular accident (CVA) Head injury Multiple sclerosis (MS) Skull base tumours Arnold-Chiari Malformation Peripheral lesions <ul style="list-style-type: none"> Unilateral <ul style="list-style-type: none"> Lung malignancy Iatrogenic injury – thyroid, parathyroid surgery, carotid endarterectomy, patent ductus arteriosus (PDA) ligation Bilateral <ul style="list-style-type: none"> Iatrogenic injury: bilateral thyroid surgery, forceps delivery Neuromuscular <ul style="list-style-type: none"> Myasthenia gravis 	
Functional	<ul style="list-style-type: none"> Psychogenic aphonia (hysterical aphonia) 	
Congenital	<ul style="list-style-type: none"> Laryngomalacia Laryngeal Web Laryngeal Atresia 	



Lung malignancy is the most common cause of vocal cord paralysis.

Neck Mass

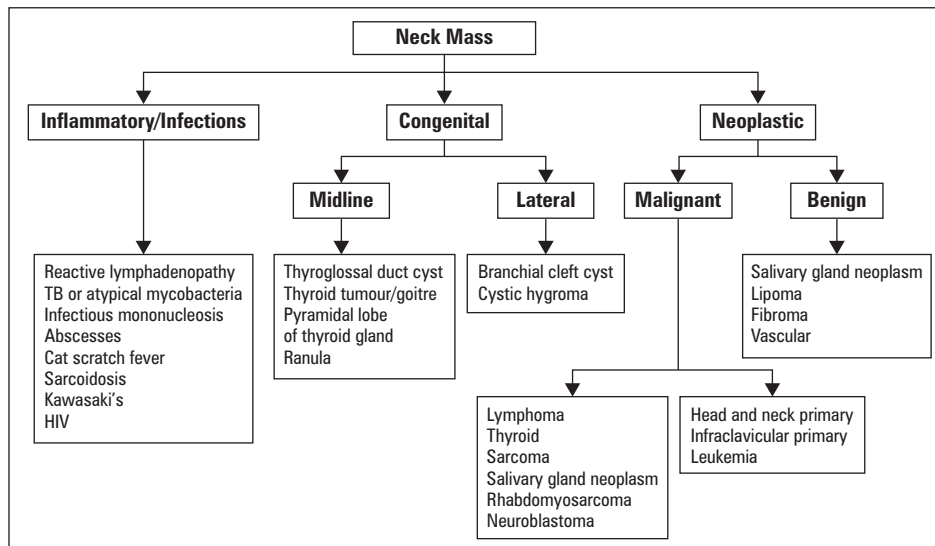


Figure 14. Differential Diagnosis of a Neck Mass

Hearing

Normal Hearing Physiology

- **Conductive pathway (External auditory canal to cochlea)** – Air conduction of sound energy down the EAC → Vibration of the tympanic membrane (area effect) → Sequential vibration of the middle ear ossicles: malleus, incus, stapes (lever effect) → Transmission of amplified vibrations from the stapes footplate in the middle ear to the oval window of the cochlea in the inner ear → Pressure differential on Cochlear fluid creates movement along the basilar membrane within the Cochlea from base to apex
- **Neural pathway (Nerve to brain)** – Basilar membrane vibration stimulates overlying hair cells in the Organ of Corti → Stimulation of bipolar neurons in the spiral ganglion of the cochlear division of CN VIII → Cochlear nucleus → Superior Olivary Nucleus → Lateral lemniscus → Inferior colliculus → Sylvian Fissure of Temporal Lobe



Order of the Neural Pathway (with corresponding waves on ABR)

E COLI

Eighth cranial nerve (I – II)
Cochlear nucleus (III)
Superior Olivary nucleus
Lateral lemniscus (IV – V)
Inferior colliculus

Types of Hearing Loss

1. Conductive Hearing Loss (CHL)

- the conduction of sound to the cochlea is impaired
- can be caused by external and middle ear disease

2. Sensorineural Hearing Loss (SNHL)

- due to a defect in the conversion of sound into neural signals or in the transmission of those signals to the cortex
- can be caused by disease of the cochlea, acoustic nerve (CN VIII), brainstem, or cortex

3. Mixed Hearing Loss

- the conduction of sound to the cochlea is impaired, as well as transmission through the cochlea to the cortex

Auditory Acuity

- whispered-voice test: mask one ear and whisper into the other
- tuning fork tests (see Table 5) (audiogram is of greater utility)
- sensitivity depends on which tuning fork used (256 Hz, 512 Hz, 1024 Hz)
 - Rinne test:
 - ♦ 512 Hz tuning fork is struck and held firmly on mastoid process to test bone conduction (BC). The tuning fork is then placed beside the pinna to test air conduction (AC)
 - ♦ If AC > BC → positive Rinne, which is normal
 - Weber test:
 - ♦ 512 Hz tuning fork is held on vertex of head and patient states whether it is heard centrally (Weber negative) or is lateralized to one side (Weber right, Weber left)
 - ♦ can place vibrating fork on patient's chin while they clench their teeth, or directly on teeth to elicit more reliable response
 - ♦ will only lateralize if difference in hearing loss between ears is >6 dB



Weber Test Lateralization = Ipsilateral conductive hearing loss or contralateral sensorineural hearing loss. When conductive hearing loss is present, the Weber test is more sensitive in detecting the CHL than the Rinne test.



HL = Intensity x Duration



Frequency of Tuning Fork (Hz)	Minimum hearing loss to have NEGATIVE Rinne (BC > AC) (dB)
256	15
512	30
1024	45

Table 5. The Interpretation of Tuning Fork Tests

Examples	Weber	Rinne
Normal or bilateral sensorineural hearing loss	Central	AC > BC (+) bilaterally
Right-sided conductive hearing loss, normal left ear	Lateralizes to Right	BC > AC (-) right
Right-sided sensorineural hearing loss, normal left ear	Lateralizes to Left	AC > BC (+) bilaterally
Right-sided severe sensorineural hearing loss or dead right ear, normal left ear	Lateralizes to Left	BC > AC (-) right*

* a vibrating tuning fork on the mastoid stimulates the cochlea bilaterally, therefore in this case, the left cochlea is stimulated by the Rinne test on the right, i.e. a false negative test. These tests are not valid if the ear canals are obstructed with cerumen (i.e. will create conductive loss)

Pure Tone Audiometry

- a threshold is the lowest intensity level at which a patient can hear the tone 50% of the time
- thresholds are obtained for each ear for frequencies 250 to 8000 Hz
- air conduction thresholds are obtained with headphones and measure outer, middle, inner ear, and auditory nerve function
- bone conduction thresholds are obtained with bone conduction oscillators which bypass the outer and middle ear

Degree of Hearing Loss

- determined on basis of the pure tone average (PTA) at 500, 1000, and 2000 Hz



Range of Frequencies Audible to Human

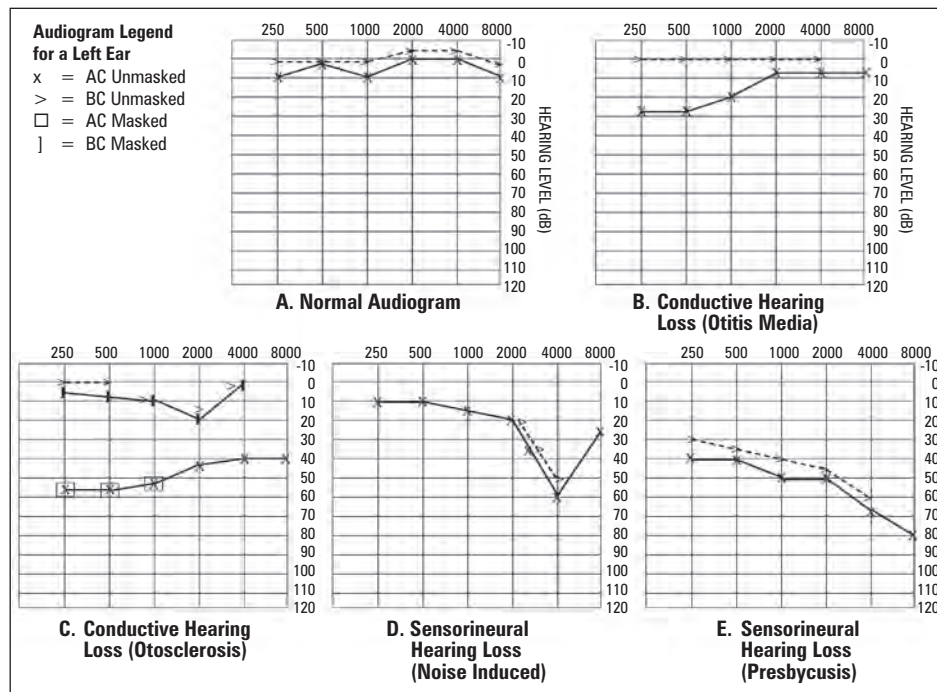
Ear: 20 to 20,000 Hz
Most sensitive frequencies: 1,000 to 4,000 Hz
Range of human speech: 500 to 2,000 Hz



Hearing loss most often occurs at higher frequencies. Noise-induced (occupational) HL is seen at 4000 Hz. HL associated with otosclerosis is seen at 2000 Hz (Carhart's notch).



Air conduction thresholds can only be equal to or greater than bone conduction thresholds.

**Figure 15. Types of Hearing Loss and Associated Audiograms of a Left Ear**

PURE TONE PATTERNS

1. Conductive Hearing Loss (CHL) (Figure 15B and 15C)

- bone conduction (BC) in normal range
- air conduction (AC) outside of normal range
- gap between AC and BC thresholds >10 dB (an air-bone gap)

2. Sensorineural Hearing Loss (SNHL) (Figure 15D and 15E)

- both air and bone conduction thresholds below normal
- gap between AC and BC <10 dB (no air-bone gap)

3. Mixed Hearing Loss

- both air and bone conduction thresholds below normal
- gap between AC and BC thresholds >10 dB (an air-bone gap)



Degree of Hearing Loss

Decibel Loss	Degree of Hearing Loss
0 to 20 dB	Normal
21 to 40 dB	Mild
41 to 55 dB	Moderate
56 to 70 dB	Moderate – Severe
71 to 90 dB	Severe
≥91 dB	Profound

Speech Audiometry

Speech Reception Threshold (SRT)

- lowest hearing level at which patient is able to repeat 50% of two syllable words which have equal emphasis on each syllable (spondee words)
- SRT and best pure tone threshold in the 500 to 2000 Hz range (frequency range of human speech) usually agree within 5 dB. If not, suspect a retrocochlear lesion or functional hearing loss
- used to assess the reliability of the pure tone audiometry

Speech Discrimination Test

- percentage of words the patient correctly repeats from a list of 50 monosyllabic words
- tested at a level 35 to 50 dB > SRT, therefore degree of hearing loss is taken into account
- patients with normal hearing or conductive hearing loss score >90%
- score depends on extent of SNHL
- rollover effect: a decrease in discrimination as sound intensity increases are typical of a retrocochlear lesion (e.g. acoustic neuroma)
- investigate further if scores differ more than 20% between ears
- used as best predictor of hearing aid response, as if patient has HL and prior word discrimination, hearing aids may not be helpful



Speech Discrimination

% of words identified	Speech Discrimination
90 to 100%	Excellent
80 to 90%	Good
60 to 80%	Fair
40 to 60%	Poor
< 40%	Very poor

Impedance Audiometry

Tympanogram

- the eustachian tube equalizes the pressure between external and middle ear
- tympanograms graph the compliance of the middle ear system against pressure gradient ranging from to -400 to +200 mmH₂O
- tympanogram peak occurs at the point of maximum compliance where the pressure in the external canal is equivalent to the pressure in the middle ear
- normal range: -100 to +50 mmH₂O

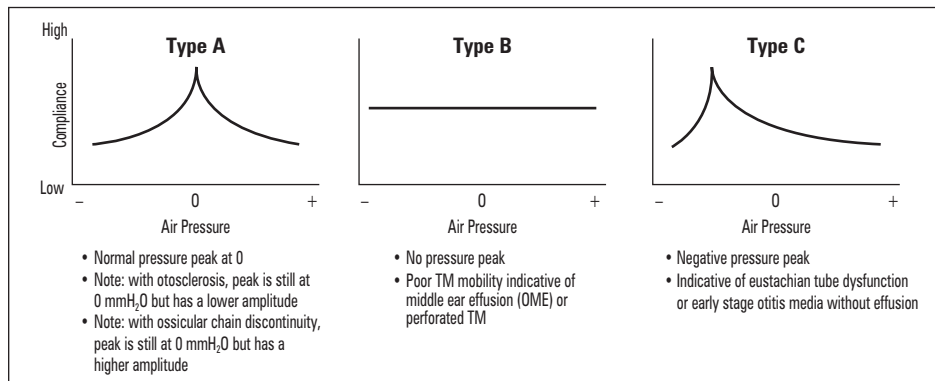


Figure 16. Tympanograms

Static Compliance

- volume measurement reflecting overall stiffness of the middle ear system
- normal range: 0.3 to 1.6 cc
- negative middle ear pressure and abnormal compliance indicate middle ear pathology
- in a type B curve, ear canal volumes of greater than 2 cc in children and 2.5 cc in adults indicate TM perforation or presence of a patent ventilation tube

Acoustic Stapedial Reflexes

- stapedius muscle contracts 2° to loud sound
- acoustic reflex thresholds** = 70 to 100 dB greater than hearing threshold; if hearing threshold >85 dB, reflex likely absent
- stimulating either ear causes bilateral and symmetrical reflexes
- for reflex to be present, CN VII must be intact and no conductive hearing loss in monitored ear
- if reflex is absent without conductive or severe sensorineural loss → suspect CN VIII lesion
- acoustic reflex decay test** = ability of stapedius muscle to sustain contraction for 10 s at 10 dB
- normally, little reflex decay occurs at 500 and 1000 Hz
- with cochlear hearing loss, acoustic reflex thresholds = 25 to 60 dB
- with retrocochlear hearing loss (acoustic neuroma) → absent acoustic reflexes or marked reflex decay (>50%) within 5 seconds

Auditory Brainstem Response (ABR)

- measures neuroelectric potentials (waves) in response to a stimulus in five different anatomic sites (refer to Order of Neural Pathway sidebar on OT9). This test can be used to map the lesion according to the site of the defect
- delay in brainstem response suggests cochlear or retrocochlear abnormalities (tumour or multiple sclerosis)
- does not require volition or co-operation of patient

Otoacoustic Emissions

- objective test of hearing where a series of clicks is presented to the ear and the cochlea generates an echo which can be measured
- often used in newborn screening
- can be used to uncover normal hearing in malingering patients

Aural Rehabilitation

- dependent on degree of hearing loss, communicative requirements, motivation, expectations, age, physical, and mental abilities
- negative prognostic factors:
 - poor speech discrimination
 - narrow dynamic range (recruitment)
 - unrealistic expectations
- types of hearing aids:
 - behind the ear
 - all in the ear
 - bone conduction – bone anchored hearing aid (BAHA): applied and attached to the skull
 - contralateral routing of signals (CROS)
- assistive listening devices:
 - direct/indirect audio output
 - infrared, FM radio, or induction loop systems
 - telephone, television, or alerting devices
- cochlear implants:
 - electrode is inserted into the cochlea to allow direct stimulation of the auditory nerve
 - for profound bilateral sensorineural hearing loss not rehabilitated with conventional hearing aids
 - established indication: post-lingually deafened adults, pre- and post-lingually deaf children



Pre-lingual deafness: deafness occurring before speech and language are acquired.

Post-lingual deafness: deafness occurring after speech and language are acquired.



Pre-lingually deaf infants are the best candidates for aural rehabilitation because they have benefitted from normal developmental plasticity.



Vertigo

Evaluation of the Dizzy Patient

- vertigo: illusion of rotational, linear, or tilting movement of self or environment
 - vertigo is produced by peripheral (inner ear) or central (brainstem-cerebellum) stimulation
- it is important to distinguish vertigo from other disease entities that may present with similar complaints of “dizziness” (e.g. cardiovascular, psychiatric, neurological, aging)

Table 6. Peripheral vs. Central Vertigo

Symptoms	Peripheral	Central
Imbalance	Mild-Moderate	Severe
Nausea and vomiting	Severe	Variable
Auditory symptoms	Common	Rare
Neurologic symptoms	Rare	Common
Compensation	Rapid	Slow
Nystagmus	Unidirectional Horizontal or rotatory	Bidirectional Horizontal or vertical

Table 7. Differential Diagnosis of Vertigo Based on History

Condition	Duration	Hearing Loss	Tinnitus	Aural Fullness	Other Features
Benign paroxysmal positional vertigo (BPPV)	Seconds	–	–	–	
Menière's disease	Minutes to hours Precedes attack	Uni/bilateral, fluctuating	+	Pressure/warmth	
Vestibular neuritis	Hours to days	Unilateral	–	–	
Labyrinthitis	Days	Unilateral	Whistling	–	Recent AOM
Acoustic neuroma	Chronic	Progressive	+	–	Ataxia CN VII palsy



Differentiate between the Following Types of Dizziness Symptoms:

- Spinning
- Lightheadedness
- Giddiness
- Unsteadiness

Benign Paroxysmal Positional Vertigo (BPPV)

Definition

- acute attacks of transient vertigo lasting **seconds to minutes** initiated by certain head positions, accompanied by torsional (i.e. rotatory) nystagmus (geotropic = fast phase towards the floor)

Etiology

- due to canalithiasis (migration of free floating otoliths within the endolymph of the semicircular canal) or cupulolithiasis (otolith attached to the cupula of the semicircular canal)
 - can affect each of the 3 semicircular canals, although the posterior canal is affected in >90% of cases
 - causes: head injury, viral infection (URTI), degenerative disease, idiopathic
 - results in slightly different signals being received by the brain from the two balance organs resulting in sensation of movement

Diagnosis

- history and positive Dix-Hallpike maneuver

Dix-Hallpike Positional Testing (see website for video and illustrations)

- the patient is rapidly moved from a sitting position to a supine position with the head hanging over the end of the table, turned to one side at 45° holding the position for 20 seconds
- onset of vertigo is noted and the eyes are observed for nystagmus
- see sidebar for the 5 signs of BPPV

Treatment

- reassure patient that process resolves spontaneously
- particle repositioning maneuvers
 - Epley maneuver (performed by MD)
 - Brandt-Daroff exercises (performed by patient)
- surgery for refractory cases
- anti-emetics for nausea/vomiting
- drugs to suppress the vestibular system delay eventual recovery and are therefore not used



BPPV is the most common cause of episodic vertigo. Patients often are symptomatic when rolling over in bed or moving their head to a position of extreme posterior extension.



5 Signs of BPPV Seen with Dix-Hallpike Maneuver

- Geotropic rotatory nystagmus (nystagmus **MUST** be present for a positive test)
- Fatigues with repeated maneuver
- Reversal of nystagmus upon sitting up
- Latency of ~20 seconds
- Crescendo/decrecendo vertigo lasting 20 seconds



Patients can wear Frenzel's magnifying eyeglasses during the Dix-Hallpike Maneuver, which inhibit visual fixation and allow for better visualization of the eyes.

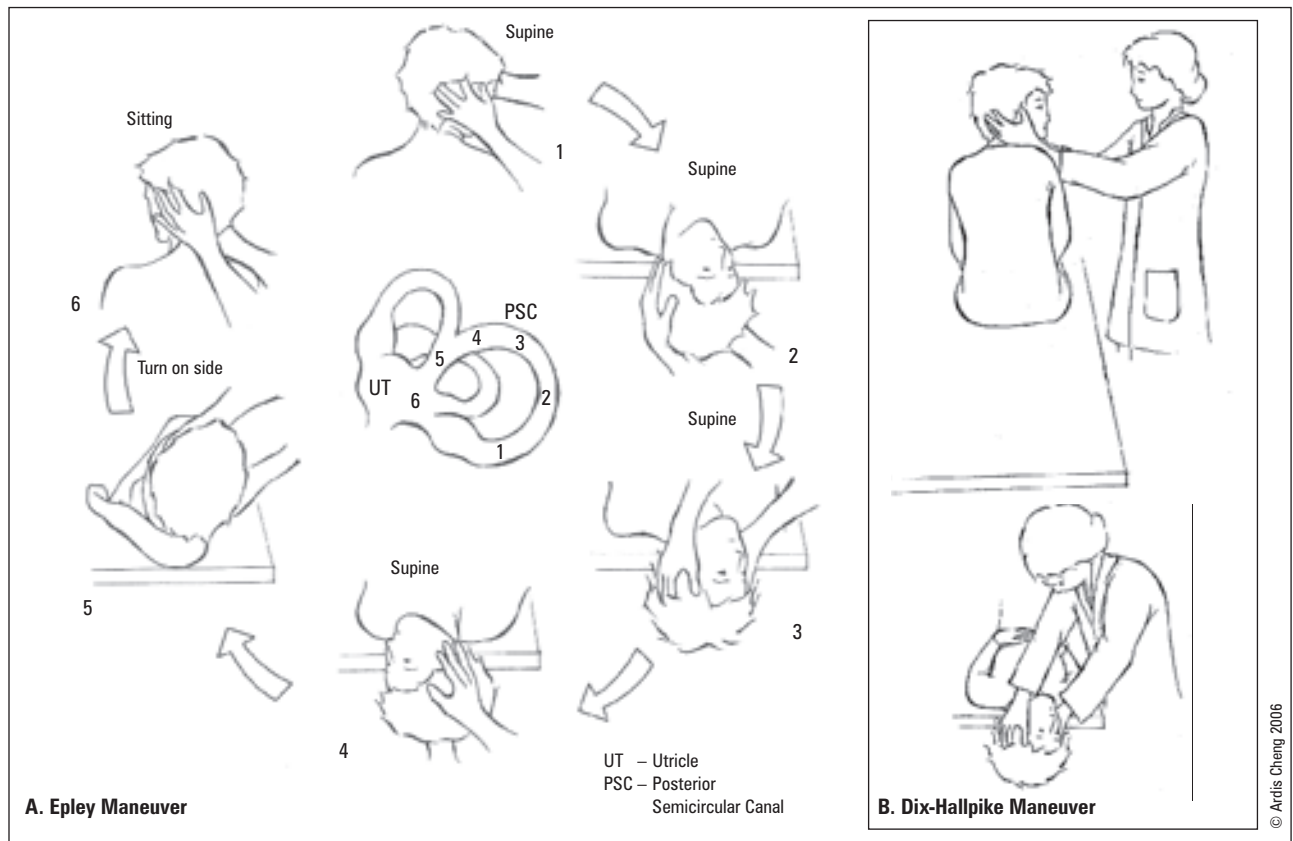


Figure 17. Epley and Dix-Hallpike Maneuvers

Menière's Disease (Endolymphatic Hydrops)

Definition

- episodic attacks of tinnitus, hearing loss, aural fullness, and vertigo lasting **minutes to hours**

Proposed Etiology

- inadequate absorption of endolymph leads to endolymphatic hydrops (over accumulation) that distorts the membranous labyrinth

Epidemiology

- peak incidence 40 to 60 years
- bilateral in 35% of cases

Clinical Features

- syndrome characterized by vertigo, fluctuating low frequency sensorineural hearing loss (SNHL), tinnitus, and aural fullness
- \pm drop attacks (Tumarkin crisis), \pm nausea and vomiting
- vertigo disappears with time (minutes to hours), but hearing loss remains
- early in the disease: fluctuating sensorineural hearing loss (SNHL)
- later stages: persistent tinnitus and low-frequency hearing loss
- attacks come in clusters and can be debilitating to the patient
- may be triggered by stress

Treatment

- acute management may consist of bed rest, antiemetics, antivertiginous drugs [e.g. betahistine (Serc®)], and low molecular weight dextrans (not commonly used)
- long term management may include:
 - medical:
 - ♦ low salt diet, diuretics (e.g. hydrochlorothiazide, triamterene, amiloride)
 - ♦ local application of gentamicin to destroy vestibular end-organ, results in complete SNHL
 - ♦ Serc® prophylactically to decrease intensity of attacks
 - surgical:
 - ♦ selective vestibular neurectomy or transtympanic labyrinthectomy
- must monitor opposite ear as bilaterality occurs in 35% of cases

Vestibular Neuronitis

Definition

- acute onset of disabling vertigo often accompanied by nausea, vomiting and imbalance without hearing loss that resolves over **days** leaving a residual imbalance that lasts days to weeks

Etiology

- thought to be due to a viral infection (e.g. measles, mumps, herpes zoster)
- ~30% of cases have associated URTI symptoms
- other: microvascular events, diabetes, autoimmune process
- considered to be the vestibular equivalent of Bell's palsy, sudden hearing loss, and acute vocal cord palsy

Clinical Features

- acute phase:
 - severe vertigo with nausea, vomiting, and imbalance lasting 1 to 5 days
 - irritative nystagmus (fast phase towards the offending ear)
 - patient tends to veer towards affected side
- convalescent phase:
 - imbalance and motion sickness lasting days to weeks
 - spontaneous nystagmus away from affected side
 - gradual vestibular adaptation requires weeks to months
- incomplete recovery likely with the following risk factors: elderly, visual impairment, poor ambulation
- repeated attacks can occur

Treatment

- acute phase:
 - bed rest, vestibular sedatives (Gravol®), diazepam
- convalescent phase:
 - progressive ambulation especially in the elderly
 - vestibular exercises: involve eye and head movements, sitting, standing, and walking



Features of Meniere's Disease
Vertigo, Tinnitus, Aural Fullness and Hearing Loss



Drop Attacks (Tumarkin's Otolithic Crisis) are sudden falls occurring without warning and without LOC.



Before proceeding with gentamicin treatment, perform a CT Head to rule out CPA tumour as the cause of symptoms.

Labyrinthitis

Definition

- acute infection of the inner ear resulting in vertigo and hearing loss

Etiology

- may be serous (viral), or purulent (bacterial)
- occurs as a complication of acute and chronic otitis media, bacterial meningitis, cholesteatoma, and temporal bone fractures
- bacterial: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *P. aeruginosa*, *P. mirabilis*
- viral: rubella, CMV, measles, mumps, varicella zoster

Clinical Features

- sudden onset of vertigo, nausea, vomiting, tinnitus, and unilateral hearing loss, with no associated fever or pain
- meningitis is a serious complication

Investigations

- CT head
- if meningitis is suspected: lumbar puncture, blood cultures

Treatment

- treat with IV antibiotics, drainage of middle ear \pm mastoidectomy

Vestibular Schwannoma (Acoustic Neuroma)

Definition

- schwannoma of the vestibular portion of CN VIII

Pathogenesis

- starts in the internal auditory canal and expands into cerebellar pontine angle (CPA), compressing cerebellum and brainstem
- when associated with type 2 neurofibromatosis (NF2): bilateral acoustic neuromas, café-au-lait skin lesions and multiple intracranial lesions

Clinical Features

- usually presents with unilateral SNHL or tinnitus
- dizziness and unsteadiness may be present, but true vertigo is rare as tumour growth occurs slowly
- facial nerve palsy and trigeminal (V₁) sensory deficit (corneal reflex) are late complications

Diagnosis

- MRI with gadolinium contrast is the gold standard
- audiogram – SNHL
- poor speech discrimination relative to the hearing loss
- stapedial reflex absent or significant reflex decay
- acoustic brainstem reflexes (ABR) – increase in latency of the 5th wave
- vestibular tests: normal or asymmetric caloric weakness (an early sign)

Treatment

- expectant management if tumour is very small, or in elderly
- definitive management is surgical excision
- other options: gamma knife, radiation



Acoustic neuroma is the most common intracranial tumour causing SNHL and the most common cerebellopontine angle tumour.



In the elderly, unilateral tinnitus or SNHL is acoustic neuroma until proven otherwise.



Hitzelberger sign: hypoesthesia of external auditory canal due to CN VII compression by an acoustic neuroma.

Tinnitus

Definition

- an auditory perception in the absence of an acoustic stimuli, likely related to loss of input to neurons in central auditory pathways and resulting in abnormal firing

History

- subjective vs. objective (see Figure 13)
- continuous vs. pulsatile (vascular in origin)
- unilateral vs. bilateral
- associated symptoms: hearing loss, vertigo, aural fullness, otalgia, otorrhea



Investigations

- audiology
- if unilateral:
 - ABR, MRI/CT to exclude a retrocochlear lesion
 - CT to diagnose glomus tympanicum (rare)
 - MRI or angiogram to diagnose AVM
- if suspect metabolic abnormality: lipid profile, TSH

Treatment

- if a cause is found, treat the cause (e.g. drainage of middle ear effusion, embolization or excision of AVM)
- with no treatable cause: 50% will improve, 25% worsen, 25% remain the same
- avoid loud noise, ototoxic meds, caffeine, smoking
- tinnitus workshops
- identify situations where tinnitus is most bothersome (e.g. quiet times), mask tinnitus with soft music or “white noise”
- hearing aid if coexistent hearing loss
- tinnitus instrument: combines hearing aid with white noise masker
- trial of tocainamide

Diseases of the External Ear

Cerumen Impaction

Etiology

- ear wax is a mixture of secretions from ceruminous and pilosebaceous glands, squames of epithelium, dust, and debris

Risk Factors

- hairy or narrow ear canals, in-the-ear hearing aids, cotton swab usage, osteomata

Clinical Features

- hearing loss (conductive)
- ± tinnitus, vertigo, otalgia, aural fullness

Treatment

- ceruminolytic drops (bicarbonate solution, olive oil, glycerine, Cerumenol®, Cerumenex®)
- syringing
- manual debridement (by MD)

Exostoses

Definition

- bony protuberances in the external auditory canal composed of lamellar bone

Etiology

- possible association with swimming in cold water

Clinical Features

- usually an incidental finding
- if large, they can cause cerumen impaction or otitis externa

Treatment

- no treatment required unless symptomatic

Otitis Externa (OE)

Etiology

- bacteria (~90% of OE): *Pseudomonas aeruginosa*, *Pseudomonas vulgaris*, *E. coli*, *S. aureus*
- fungus: *Candida albicans*, *Aspergillus niger*

Risk Factors

- associated with swimming (“swimmer’s ear”)
- mechanical cleaning (Q-tips®), skin dermatitides, aggressive scratching
- devices that occlude the ear canal: hearing aids, headphones, etc.



Cerumen impaction is the most common cause of conductive hearing loss for those aged 15-50 years.

**Syringing****Indications:**

- Totally occlusive cerumen with pain, decreased hearing, or tinnitus

Contraindications:

- Non-occlusive cerumen
- Previous ear surgery
- Only hearing ear
- TM perforation

Complications:

- Failure
- Otitis externa
- TM perforation
- Trauma
- Pain
- Vertigo
- Tinnitus
- Otitis media

Method:

- Establish that TM is intact
- Gently pull the pinna superiorly and posteriorly
- Using warm water, aim the syringe nozzle upwards and posteriorly to irrigate the ear canal



Clinical Features

- acute:
 - pain aggravated by movement of auricle (traction of pinna or pressure over tragus)
 - otorrhea (sticky yellow purulent discharge)
 - conductive hearing loss \pm aural fullness 2° to obstruction of external canal by swelling and purulent debris
 - post-auricular lymphadenopathy
 - complicated OE exists if the pinna and/or the periauricular soft tissues are erythematous and swollen
- chronic:
 - pruritus of external ear \pm excoriation of ear canal
 - atrophic and scaly epidermal lining, \pm otorrhea, \pm hearing loss
 - wide meatus but no pain with movement of auricle
 - tympanic membrane appears normal



Pulling on the pinna is extremely painful in otitis externa, but is usually well tolerated in otitis media.

Treatment

- clean ear under magnification with irrigation, suction, dry swabbing, and C&S
- bacterial etiology
 - antipseudomonal otic drops (e.g. gentamicin, ciprofloxacin) or a combination of antibiotic and steroid (e.g. Garasone® or Cipro HC®)
 - do not use aminoglycoside if the tympanic membrane (TM) is perforated because of the risk of ototoxicity
 - introduction of fine gauze wick (pope wick) if external canal edematous
 - \pm 3% acetic acid solution to acidify ear canal (low pH is bacteriostatic)
 - systemic antibiotics if either cervical lymphadenopathy or cellulitis
- fungal etiology
 - repeated debridement and topical antifungals (gentian violet, Mycostatin® powder, boric acid, Locacorten®, Vioform® drops)
- \pm analgesics
- chronic otitis externa (pruritus without obvious infection) \rightarrow corticosteroid alone e.g. diprosalic acid

Malignant (Necrotizing) Otitis Externa (Skull Base Osteomyelitis)

**Definition**

- osteomyelitis of the temporal bone

Epidemiology

- occurs in elderly diabetics and immunocompromised patients

Etiology

- rare complication of otitis externa
- *Pseudomonas* infection in 99% of cases

Clinical Features

- otalgia and purulent otorrhea that is refractory to medical therapy
- granulation tissue on the floor of the auditory canal

Complications

- lower cranial nerve palsies
- systemic infection, death

Management

- imaging: high resolution temporal bone CT scan, gadolinium scan, technetium scan
- requires hospital admission, debridement, IV antibiotics, hyperbaric O₂
- may require OR for debridement of necrotic tissue/bone

**Gallium and Technetium Scans**

Gallium scans are used to show sites of active infection. Gallium is taken up by PMNs and therefore only lights up when active infection is present. It will not show the extent of osteomyelitis. Technetium scans provide information about osteoblastic activity and as such are used to demonstrate sites of osteomyelitis. Technetium scans help with diagnosis whereas gallium scans are useful in follow-up.

Diseases of the Middle Ear

Acute Otitis Media (AOM) and Otitis Media with Effusion (OME)



- see *Pediatric Otolaryngology*, OT38



Cholesteatoma

Definition

- a cyst composed of keratinizing squamous epithelium occurring in the middle ear, mastoid and temporal bone
- two types: congenital and acquired (see below)

Congenital

- presents as a “small white pearl” behind an intact tympanic membrane (anterior and medial to the malleus) or as a conductive hearing loss
- believed to be due to aberrant migration of external canal ectoderm during development
- not associated with otitis media/eustachian tube dysfunction

Acquired (more common)

- generally occurs as a consequence of otitis media and chronic eustachian tube dysfunction
- frequently associated with retraction pockets in the pars flaccida (1° acquired) and marginal perforations (2° acquired) of the tympanic membrane
- the associated chronic inflammatory process causes progressive destruction of surrounding bony structures

Clinical Features

- symptoms:
 - history of otitis media (especially if unilateral), ventilation tubes, ear surgery
 - progressive hearing loss (predominantly conductive although may get sensorineural hearing loss in late stage)
 - otalgia, aural fullness, fever
- signs:
 - retraction pocket in TM, may contain keratin debris
 - TM perforation
 - granulation tissue, polyp visible on otoscopy
 - malodorous, unilateral otorrhea

Complications

Table 8. Complications of Cholesteatoma

Local	Intracranial
Ossicular erosion: conductive hearing loss	Meningitis
Inner ear erosion: SNHL, dizziness and/or labyrinthitis	Sigmoid sinus thrombosis
Temporal bone infection: mastoiditis, petrositis	Intracranial abscess (subdural, epidural, cerebellar)
Facial paralysis	

Investigations

- audiogram and CT scan

Treatment

- there is no conservative therapy for cholesteatoma
- surgical: mastoidectomy ± tympanoplasty ± ossicular reconstruction



Mechanisms of Cholesteatoma Formation

1. Epithelial migration through TM perforation (2° acquired)
2. Invagination of TM (1° acquired)
3. Metaplasia of middle ear epithelium (congenital)
4. Basal cell hyperplasia (congenital)



Mastoiditis

Definition

- complication of AOM
- infection (usually subperiosteal) of mastoid air cells, most commonly seen approximately two weeks after onset of untreated or inadequately treated acute suppurative otitis media

Etiology

- acute mastoiditis caused by the same organisms as AOM: *S. pneumoniae*, *S. pyogenes*, *S. aureus*, *H. influenzae*

Clinical Features

- classic triad
 - otorrhea
 - tenderness to pressure over the mastoid
 - retroauricular swelling with protruding ear
- fever, hearing loss, ± TM perforation (late)
- CT radiologic findings: opacification of mastoid air cells by fluid and interruption of normal trabeculations of cells



Mastoiditis is now rare due to rapid and effective treatment of acute otitis media with antibiotics.

Treatment

- IV antibiotics with myringotomy and ventilation tubes – usually all that is required acutely
- cortical mastoidectomy:
 - debridement of infected tissue allowing aeration and drainage
- indications for surgery:
 - failure of medical treatment after 48 hours
 - symptoms of intracranial complications
 - aural discharge persisting for 4 weeks and resistant to antibiotics

Otosclerosis**Definition**

- fusion of stapes footplate to oval window so that it cannot vibrate

Etiology

- autosomal dominant, variable penetrance approximately 40%
- female > male, progresses during pregnancy (hormone responsive)

Clinical Features

- progressive conductive hearing loss first noticed in teens and 20's (may progress to sensorineural hearing loss if cochlea involved)
- \pm pulsatile tinnitus
- tympanic membrane normal \pm pink blush (Schwartz's sign) associated with the neovascularization of otosclerotic bone
- characteristic dip at 2,000 Hz (Carhart's notch) on audiogram (see Figure 15)



Otosclerosis is the 2nd most common cause of conductive hearing loss in 15 to 50 year olds (after cerumen impaction).

Treatment

- monitor with serial audiograms if coping with loss
- hearing aid (air conduction, bone conduction, BAHA)
- stapedectomy or stapedotomy (with laser or drill) with prosthesis is definitive treatment

Diseases of the Inner Ear**Congenital Sensorineural Hearing Loss****Hereditary Defects**

- non-syndrome associated (70%):
 - often idiopathic, autosomal recessive
 - connexin 26 (GJB2) most common
- syndrome associated (30%):
 - Waardenburg's – white forelock, heterochromia iridis, wide nasal bridge and increased distance between medial canthi
 - Pendred's – deafness associated with thyroid gland disorders, SLC26A4 gene, enlarged vestibular aqueducts
 - Treacher-Collins – first and second branchial cleft anomalies
 - Alport's – hereditary nephritis

Prenatal TORCH Infections

- toxoplasmosis, rubella, cytomegalovirus (CMV), herpes simplex, others (e.g. HIV, syphilis)

Perinatal

- Rh incompatibility
- anoxia
- hyperbilirubinemia
- birth trauma (hemorrhage into inner ear)

Postnatal

- meningitis
- mumps
- measles

High Risk Registry (for Hearing Loss in Newborns)

- risk factors:
 - low birth weight/prematurity
 - perinatal anoxia (low APGARs)
 - kernicterus – bilirubin >25 mg/dL
 - craniofacial abnormality
 - family history of deafness in childhood



Congenital SNHL is decreasing in incidence due to the availability of vaccines and improved neonatal care.

- 1st trimester illness – TORCH infections
- neonatal sepsis
- ototoxic drugs
- perinatal infection, including post-natal meningitis
- consanguinity
- 50-75% of newborns with sensorineural hearing loss have at least one of the above risk factors, and 90% of these have spent time in the NICU
- presence of any risk factor: auditory brainstem response (ABR) study performed before leaving NICU and at 3 months adjusted age
- early rehabilitation improves speech and school performance

Presbycusis

Definition

- sensorineural hearing loss associated with aging (staging in 5th and 6th decades)

Etiology

- hair cell degeneration
- age related degeneration of basilar membrane
- cochlear neuron damage
- ischemia of inner ear

Clinical Features

- progressive, gradual bilateral hearing loss initially at high frequencies, then middle frequencies
- loss of discrimination of speech especially with background noise present – patients describe people as mumbling
- recruitment phenomenon: inability to tolerate loud sounds
- tinnitus

Treatment

- hearing aid if patient has difficulty functioning, hearing loss >30-35 dB, and good speech discrimination
- ± lip reading, auditory training, auditory aids (doorbell and phone lights)



Presbycusis is the most common cause of SNHL.

Sudden Sensorineural Hearing Loss

Clinical Features

- presents as a sudden onset of significant SNHL (usually unilateral) ± tinnitus, aural fullness
- usually idiopathic, rule out other causes:
 - autoimmune causes – ESR, rheumatoid factor, ANA
 - MRI to rule out tumour and/or CT to rule out ischemic/hemorrhagic stroke if associated with any other focal neurological signs (e.g. vertigo, ataxia, abnormality of CN V or VII, weakness)

Treatment

- treat with oral corticosteroids within 3 days of onset: prednisone 1-2 mg/kg/day, tapering over 2 weeks

Prognosis

- depends on degree of hearing loss
- 70% resolve spontaneously within 10 to 14 days
- 20% experience partial resolution
- 10% experience permanent hearing loss

Autoimmune Inner Ear Disease

Etiology

- idiopathic
- may be associated with systemic autoimmune diseases (ie. rheumatoid arthritis, SLE), vasculitides (i.e. Wegener's, polyarteritis nodosa) and allergies

Epidemiology

- most common between ages 20-50

Clinical Features

- rapidly progressive or fluctuating bilateral SNHL
- ± tinnitus, aural fullness, vestibular symptoms (i.e. ataxia, disequilibrium, vertigo)



Sudden sensorineural hearing loss may easily be confused with ischemic brain events. It is important to keep a high index of suspicion especially with elderly patients presenting with sudden sensorineural hearing loss as well as vertigo.

Investigations

- autoimmune work-up: CBC, ESR, ANA, rheumatoid factor

Treatment

- high-dose corticosteroids: treat early for at least 30 days
- consider cytotoxic medication for steroid non-responders

Drug Ototoxicity**Aminoglycosides**

- toxic to hair cells by any route: oral, IV, and topical (if the TM is perforated)
- destroys sensory hair cells – outer first, inner second (therefore OAEs are lost first)
- high frequency hearing loss develops earliest
- ototoxicity occurs days to weeks post-treatment
- streptomycin and gentamicin (vestibulotoxic), kanamycin and tobramycin (cochleotoxic)
- must monitor with peak and trough levels when prescribed, especially if patient has neutropenia and/or history of ear or renal problems
- q24h dosing recommended, with amount determined by creatinine clearance, not serum creatinine
- aminoglycoside toxicity displays saturable kinetics therefore once daily dosing presents less risk than divided daily doses
- duration of treatment is the most important predictor of ototoxicity
- treatment: immediately stop aminoglycosides

Salicylates

- hearing loss with tinnitus, reversible if discontinued

Antimalarials (Quinine)

- hearing loss with tinnitus
- reversible if discontinued but can lead to permanent loss

Others

- many antineoplastics agent are ototoxic (weigh risks vs. benefits)
- loop diuretics

Noise-Induced Sensorineural Hearing Loss**Pathogenesis**

- 85 to 90 dB over months or years causes cochlear damage
- early-stage hearing loss at 4000 Hz (because this is the resonance frequency of the temporal bone), extends to higher and lower frequencies with time (see Figure 15D)
- speech reception not altered until hearing loss >30 dB at speech frequency, therefore considerable damage may occur before patient complains of hearing loss
- difficulty with speech discrimination, especially in situations with competing noise



Short exposures to louder sounds can cause significant SNHL.

Phases of Hearing Loss

- dependent on: intensity of sound and duration of exposure
- temporary threshold shift:
 - when exposed to loud sound, decreased sensitivity or increased threshold for sound
 - may have associated aural fullness and tinnitus
 - with removal of noise, hearing returns to normal
- permanent threshold shift:
 - hearing does not return to previous state



Limits of Noise Causing Damage
Continuous sound pressure >85 dB
Single sound impulse >135 dB

Treatment

- hearing aid
- prevention:
 - ear protectors: muffs, plugs
 - machinery which produces less noise
 - limit exposure to noise with frequent rest periods
 - regular audiologic follow-up

Inner Ear Diseases that cause Vertigo

- see *Vertigo*, OT12
 - benign paroxysmal positional vertigo (BPPV)
 - Menière's disease (endolymphatic hydrops)
 - vestibular neuronitis
 - labyrinthitis
 - acoustic neuroma (AN), (vestibular schwannoma)

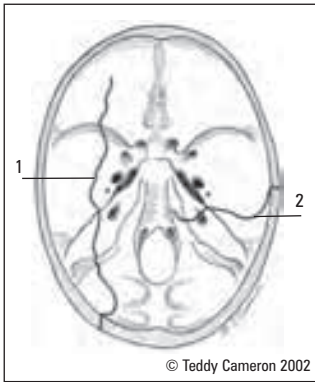


Figure 18. Types of Temporal Bone Fractures



Signs of Basilar Skull Fracture

Battle's Sign: ecchymosis of the mastoid process of the temporal bone

Raccoon Eyes

CSF Rhinorrhea/Otorrhea

Cranial Nerve involvement (facial palsy → CN VII, nystagmus → CN VI, facial numbness → CN V)



The halo sign is the double ringed appearance of CSF fluid on white filter paper as it separates out from blood.



Hemotympanum can be indicative of temporal bone trauma.



House-Brackmann Facial Nerve Grading System

Grade I: Normal facial motor function

Grade II: Mild dysfunction
– Slight weakness
– Normal symmetry and tone at rest
– Complete eye closure

Grade III: Moderate dysfunction
– Obvious weakness

Grade IV: Moderately severe dysfunction
– Obvious weakness
± disfiguring asymmetry
– Incomplete eye closure
– No forehead motion
– Mouth asymmetric motion

Grade V: Severe dysfunction
– Barely perceptible motion of mouth
– Asymmetric at rest

Grade VI: Total paralysis
– No movement

Temporal Bone Fractures

- rarely are temporal bone fractures purely transverse or longitudinal, often it is a mixed picture

Table 9. Features of Temporal Bone Fractures (see Figure 18)

	Transverse (1)	Longitudinal (2)
Extension	Into bony labyrinth and internal auditory meatus	Into middle ear
Incidence	10 to 20%	70 to 90%
Etiology	Frontal/occipital trauma	Lateral skull trauma
CN pathology	CN VII palsy (50%)	CN VII palsy (10 to 20%)
Hearing loss	Sensorineural loss due to direct cochlear injury	Conductive hearing loss secondary to ossicular injury
Vestibular symptoms	Sudden onset vestibular symptoms due to direct semicircular canal injury (vertigo, spontaneous nystagmus)	Rare
Other features	Intact external auditory meatus, tympanic membrane ± hemotympanum Spontaneous nystagmus CSF leak in eustachian tube to nasopharynx ± rhinorrhea (risk of meningitis)	Torn tympanic membrane or hemotympanum Bleeding from external auditory canal Step formation in external auditory canal CSF otorrhea Battle's sign = mastoid ecchymoses Raccoon eyes = periorbital ecchymoses

* Classic types of fractures are uncommon with modern injury (MVA); often see a combination of pure types

Diagnosis

- otoscopy
- do not syringe or manipulate external auditory meatus due to risk of inducing meningitis via TM perforation
- CT head
- audiology, facial nerve tests (for transverse fractures), Schirmer's test (of lacrimation), stapedial reflexes if CN VII palsy
- if suspecting CSF leak: look for halo sign (see sidebar), send fluid for beta-2-transferrin

Treatment

- ABC's
- medical – expectant, prevent otogenic meningitis
- surgical – explore temporal bone, indications:
 - CN VII palsy (immediate and complete)
 - gunshot wound
 - depressed fracture of external auditory meatus
 - early meningitis (mastoidectomy)
 - bleeding intracranially from sinus
 - CSF otorrhea (may resolve spontaneously)

Complications

- acute otitis media ± labyrinthitis ± mastoiditis
- meningitis/epidural abscess/brain abscess
- post-traumatic cholesteatoma

Facial Nerve (CN VII) Paralysis

Etiology

- supranuclear and nuclear (MS, poliomyelitis, cerebral tumours)
- infranuclear – see table below

Treatment

- treat according to etiology plus provide corneal protection with artificial tears, nocturnal lid taping, tarsorrhaphy, gold weighting of upper lid
- facial paralysis that does not resolve with time or with medical treatment will often be referred for possible reanimation techniques to restore function
 - common reanimation techniques include:
 - ♦ direct facial nerve anastomosis
 - ♦ interpositional grafts
 - ♦ anastomosis to other motor nerves
 - ♦ muscle transpositions

Table 10. Differential Diagnosis of Peripheral Facial Paralysis (PFP)

Etiology	Incidence	Findings	Investigations	Treatment, Follow-up, and Prognosis (Px)
Bell's Palsy Idiopathic, (HSV) infection of the facial nerve Diagnosis of exclusion	80 to 90% of PFP Risk Factors: Diabetes Pregnancy Viral prodrome (50%)	Hx: Acute onset Numbness of ear Schirmer's test Recurrence (12%) + FHx (14%) Hyperacusis (30%) P/E: Paralysis or paresis of all muscle groups on one side of the face Absence of signs of CNS disease Absence of signs of ear or CPA diseases	Stapedial reflex absent Audiology normal (or baseline) Electromyogram (EMG) – best measure for prognosis Topographic testing MRI with gadolinium – enhancement of CN VII and VIII High resolution CT	Rx: Protect the eye to prevent exposure keratitis with patching or tarsorrhaphy Systemic steroids may lessen degeneration and hasten recovery Consider antiviral (acyclovir) F/U: Spontaneous remission should begin within 3 weeks of onset Delayed (3 to 6 months) recovery portends at least some functional loss Px: 90% recover spontaneously and completely overall; >90% recovery if paralysis was incomplete Poorer if hyperacusis, >60 yrs, diabetes, HTN, severe pain
Ramsay-Hunt Syndrome (Herpes Zoster Oticus) Varicella zoster infection of CN VII/VIII	4.5 to 9% of PFP Risk Factors: >60 years Impaired immunity Cancer Radiotherapy Chemotherapy (see OT22)	Hx: Hyperacusis SNHL Severe pain of pinna, mouth, or face P/E: Vesicles on pinna, ext. canal (erupt 3-7 days after onset of pain) Associated herpes zoster ophthalmicus (uveitis, keratoconjunctivitis, optic neuritis, or glaucoma)	Stapedial reflex absent Audiology – SNHL Viral ELISA studies to confirm MRI with gadolinium (86% of facial nerves enhance)	Rx: Pt. should avoid touching lesions to prevent spread of infection Systemic steroids can relieve pain, vertigo, avoid postherpetic neuralgia Acyclovir may lessen pain, aid healing of vesicles F/U: 2 to 4 weeks Px: Poorer prognosis than Bell's palsy; 22% recover completely, 66% incomplete paralysis, 10% complete paralysis
Temporal Bone Fracture				
Longitudinal (90%)	20% have PFP	Hx: Blow to side of head P/E: Trauma to side of head Neuro findings consistent with epidural/subdural bleed	Skull X-rays CT head	Px: Injury usually due to stretch or impingement; may recover with time
Transverse (10%)	40% have PFP	Hx: Blow to frontal or occipital area P/E: Trauma to front or back of head	Skull X-rays CT head	Px: Nerve transection more likely
Iatrogenic		Variable (depending on level of injury)	Wait for lidocaine to wear off EMG	Rx: Exploration if complete nerve paralysis No exploration if any movement present

Source: Paul Warrick. icarus.med.utoronto.ca/carr/manual/afnptable.html

Rhinitis

Definition

- inflammation of the lining (mucosa) of the nasal cavity

Table 11. Classification of Rhinitis

Inflammatory	Non-Inflammatory
<ul style="list-style-type: none"> • Perennial non-allergic <ul style="list-style-type: none"> • Asthma, ASA sensitivity • Allergic <ul style="list-style-type: none"> • Seasonal • Perennial • Atrophic <ul style="list-style-type: none"> • Primary: <i>Klebsiella ozena</i> (especially in elderly) • Acquired: post-surgery if too much mucosa or turbinate has been resected • Infectious <ul style="list-style-type: none"> • Viral: e.g. rhinovirus, influenza, parainfluenza, etc. • Bacterial: e.g. <i>S. aureus</i> • Fungal • Granulomatous: TB, syphilis, leprosy • Non-infectious <ul style="list-style-type: none"> • Sarcoidosis • Wegener's granulomatosis • Irritant <ul style="list-style-type: none"> • Dust • Chemicals • Pollution 	<ul style="list-style-type: none"> • Rhinitis medicamentosa <ul style="list-style-type: none"> • Topical decongestants • Hormonal <ul style="list-style-type: none"> • Pregnancy • Estrogens • Thyroid • Idiopathic vasomotor



Rhinitis medicamentosa is rebound congestion due to the overuse of intranasal vasoconstrictors. For prevention, use of these medications for only 5-7 days is recommended.

Table 12. Nasal Discharge: Character and Associated Conditions

Character	Associated Conditions
Watery/mucoid	Allergic, viral, vasomotor, CSF leak (halo sign)
Mucopurulent	Bacterial, foreign body
Serosanguinous	Neoplasia
Bloody	Trauma, neoplasia, bleeding disorder, hypertension/vascular disease

Allergic Rhinitis (Hay Fever)

Definition

- rhinitis characterized by an IgE-mediated hypersensitivity to foreign allergens
- acute-and-seasonal or chronic-and-perennial
- perennial allergic rhinitis often confused with recurrent colds

Etiology

- when allergens contact the respiratory mucosa, specific IgE antibody is produced in susceptible hosts
- concentration of allergen in the ambient air correlates directly with the rhinitis symptoms

Epidemiology

- age at onset usually <20 years
- more common in those with a personal or family history of allergies/atopy

Clinical Features

- nasal: obstruction with pruritus, sneezing
- clear rhinorrhea (containing increased eosinophils)
- itching of eyes with tearing
- frontal headache and pressure
- mucosa – swollen, pale, lavender colour, and “boggy”
- seasonal (summer, spring, early autumn)
 - pollens from trees
 - lasts several weeks, disappears and recurs following year at same time
- perennial
 - inhaled: house dust, wool, feathers, foods, tobacco, hair, mould
 - ingested: wheat, eggs, milk, nuts
 - occurs intermittently for years with no pattern or may be constantly present

Complications

- chronic sinusitis/polyps
- serous otitis media

Diagnosis

- history
- direct exam
- allergy testing

Treatment

- education: identification and avoidance of allergen
- nasal irrigation with saline
- antihistamines e.g. diphenhydramine, fexofenadine
- oral decongestants e.g. pseudoephedrine, phenylpropanolamine
- topical decongestant may lead to rhinitis medicamentosa
- other topicals: steroids (fluticasone), disodium cromoglycate, antihistamines, ipratropium bromide
- oral steroids if severe
- desensitization by allergen immunotherapy

Vasomotor Rhinitis

- neurovascular disorder of nasal parasympathetic system (vidian nerve) affecting mucosal blood vessels
- nonspecific reflex hypersensitivity of nasal mucosa
- caused by:
 - temperature change
 - alcohol, dust, smoke
 - stress, anxiety, neurosis



Congestion reduces nasal airflow and allows the nose to repair itself. Treatment should focus on the initial insult rather than target this defense mechanism.

- endocrine – hypothyroidism, pregnancy, menopause
- parasympathomimetic drugs
- beware of rhinitis medicamentosa: reactive vasodilation due to prolonged use (>5 days) of nasal drops and sprays (Dristan®, Otrivin®)

Clinical Features

- chronic intermittent nasal obstruction, varies from side to side
- rhinorrhea: thin, watery
- nasal allergy must be ruled out
- mucosa and turbinates: swollen, pale between exposure
- symptoms are often more severe than clinical presentation suggests

Treatment

- elimination of irritant factors
- parasympathetic blocker (Atrovent® nasal spray)
- steroids (e.g. beclomethasone, fluticasone)
- surgery (often of limited lasting benefit): electrocautery, cryosurgery, laser treatment or removal of inferior or middle turbinates
- vidian neurectomy (rarely done)
- symptomatic relief with exercise (increased sympathetic tone)

Sinusitis

Development of Sinuses

- sinus pneumatization begins in 3rd-4th month of fetal life
- maxillary sinus first to develop
- neonate – clinically significant ethmoid and maxillary buds present
- age 9 – maxillary full grown; frontal and sphenoid cells starting
- age 18 – frontal and sphenoid cells full grown

Pathogenesis of Sinusitis

- inflammation of the mucosal lining of the paranasal sinuses
- anything that blocks mucus from exiting the sinuses predisposes them to inflammation
- all sinuses drain to a common prechamber under the middle meatus called the osteomeatal complex

Definition

- inflammation of the mucosal lining of the sinuses

Classification

- acute: <4 weeks
- subacute: 4 weeks to 3 months
- chronic: >3 months

Table 13. Etiologies of Sinusitis

Ostial Obstruction	Inflammation	<ul style="list-style-type: none"> • URTI • Allergy
	Mechanical	<ul style="list-style-type: none"> • Septal deviation • Turbinate hypertrophy • Polyps • Tumours • Adenoid hypertrophy • Foreign body • Congenital abnormalities i.e. cleft palate
	Immune	<ul style="list-style-type: none"> • Wegener's granulomatosis • Lymphoma, leukemia • Immunosuppressed patients (e.g. neutropenics, diabetics, HIV)
	Systemic	<ul style="list-style-type: none"> • Cystic fibrosis • Immotile cilia (Kartagener's)
Direct Extension	Dental	<ul style="list-style-type: none"> • Infection
	Trauma	<ul style="list-style-type: none"> • Facial fractures



FESS = Functional Endoscopic Sinus Surgery

Opening of the entire osteomeatal complex in order to facilitate drainage while sparing the sinus mucosa.

Acute Suppurative Sinusitis

Definition

- acute infection and inflammation of the paranasal sinuses
- clinical diagnosis requiring at least 2 major symptoms or 1 major and 2 minor symptoms
 - **major symptoms**
 - ♦ facial pain/pressure
 - ♦ facial fullness/congestion
 - ♦ nasal obstruction
 - ♦ purulent/discholoured nasal discharge
 - ♦ hyposmia/anosmia
 - ♦ fever
 - **minor symptoms**
 - ♦ headache
 - ♦ halitosis
 - ♦ fatigue
 - ♦ dental pain
 - ♦ cough
 - ♦ ear pressure/fullness



Acute Sinusitis Complications

Consider hospitalization if any of the following are suspected

1. Orbital (Chandler's classification)
 - a. Periorbital cellulitis
 - b. Orbital cellulitis
 - c. Subperiosteal abscess
 - d. Orbital abscess
 - e. Cavernous sinus thrombosis
2. Intracranial
 - a. Meningitis
 - b. Abscess
3. Bony
 - a. Subperiosteal frontal bone abscess ("Pott's Puffy Tumour")
 - b. Osteomyelitis
4. Neurologic
 - a. Superior orbital fissure syndrome
CN III/IV/VI palsy, immobile globe, dilated pupils, ptosis, V1 hypoaesthesia)
 - b. Orbital apex syndrome
(as "4a" above, plus neuritis, papilledema, decreased acuity)

Etiology

- viral vs. bacterial (viral etiology is more common)
- children are more prone to a bacterial etiology, but viral is still more common
- maxillary sinus most commonly affected
- must rule out fungal causes (mucormycosis) in immunocompromised hosts (especially if painless, bloodless mucosa on examination)
- organisms
 - viral: rhinovirus, influenza, parainfluenza
 - bacterial: *S. pneumoniae* (35%), *H. influenzae* (35%), *M. catarrhalis*, anaerobes (dental)

Clinical Features

- sudden onset of
 - nasal blockage/congestion and/or
 - nasal discharge/posterior nasal drip
- ± facial pain or pressure, hyposmia
- signs more suggestive of a bacterial etiology are erythematous nasal mucosa, mucopurulent discharge, pus originating from the middle meatus and the presence of nasal polyps or a deviated septum
- acute viral rhinosinusitis lasts <10 days
- if symptoms increase after 5 days or persist >10 days, consider bacterial etiology

Management

- anterior rhinoscopy
- x-ray/CT scan not recommended unless complications are suspected (i.e. sub-periorbital abscess or intracranial spread – Pott's Puffy tumour)
- symptoms improving within 5 days: symptomatic relief and expectant management
- moderate symptoms that worsen or persist beyond 5 days: institute an intranasal corticosteroid spray and continue for 14 days if symptomatic relief is noted within 48 hrs
- severe symptoms that worsen or persist beyond 5 days and are refractory to intranasal corticosteroid (INCS): clarithromycin or Clavulin® therapy ± INCS ± referral to a specialist
- surgery if medical therapy fails: FESS

Chronic Sinusitis

Definition

- inflammation of the paranasal sinuses **lasting >3 months**

Etiology

- can result from any of the following:
 - inadequate treatment of acute sinusitis
 - untreated nasal allergy
 - allergic fungal rhinosinusitis
 - anatomic abnormality e.g. deviated septum (predisposing factor)
 - underlying dental disease
 - ciliary disorder e.g. cystic fibrosis, Kartagener's
 - chronic inflammatory disorder e.g. Wegener's
- organisms:
 - bacterial: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. pyogenes*, *S. aureus*, anaerobes
 - fungal: *Aspergillus*

Clinical Features (similar to acute, but less severe)

- chronic nasal obstruction
- purulent nasal discharge
- pain over sinus or headache



Allergic fungal rhinosinusitis is a chronic sinusitis affecting mostly young, immunocompetent, atopic individuals. Treatment options include FESS ± intranasal topical steroids, antifungals and immunotherapy.



Chronic Sinusitis Complications

1. Polyps
2. Mucocoele

- halitosis
- yellow-brown post-nasal discharge
- chronic cough
- maxillary dental pain

Treatment

- antibiotics for 3 to 6 weeks for infectious etiology
 - augmented penicillin (Clavulin®), macrolide (clarithromycin), fluoroquinolone (levofloxacin), clindamycin, Flagyl®
- topical nasal steroid, saline spray
- surgery if medical therapy fails or fungal sinusitis

Surgical Treatment

- functional endoscopic sinus surgery → open osteomeatal complex
- balloon sinuplasty

Epistaxis

Blood Supply to the Nasal Septum (Figure 4)

1. Superior posterior septum:
 - internal carotid → ophthalmic → anterior/posterior ethmoidal
 2. Posterior septum:
 - external carotid → internal maxillary → sphenopalatine artery → nasopalatine
 3. Lower anterior septum:
 - external carotid → facial artery → superior labial artery → nasal branch
 - external carotid → internal maxillary → descending palatine → greater palatine
- these arteries all anastomose to form Kiesselbach's plexus, located at Little's area (anterior portion of the cartilaginous septum)
 - bleeding from above middle turbinate is internal carotid, and from below is external carotid



90% of nose bleeds occur in Little's area.

Table 14. Etiology of Epistaxis

Type	Causes
Local	Trauma (most common) <ul style="list-style-type: none"> • Fractures: facial, nasal • Self-induced: digital, foreign body
	Iatrogenic: nasal, sinus, orbit surgery
	Barometric changes
	Nasal dryness: dry air, ± septal deformities
	Septal perforation
	Chemical: cocaine, nasal sprays, ammonia, etc.
Systemic	Tumours <ul style="list-style-type: none"> • Benign: polyps, inverting papilloma, angiofibroma • Malignant: squamous cell carcinoma, esthesioneuroblastoma
	Inflammation <ul style="list-style-type: none"> • Rhinitis: allergic, non-allergic • Infections: bacterial, viral, fungal
	Idiopathic
	Coagulopathies <ul style="list-style-type: none"> • Meds: anticoagulants, NSAIDs • Hemophilias, von Willebrand's • Hematological malignancies • Liver failure, uremia
	Vascular: hypertension, atherosclerosis, Osler-Weber-Rendu (HHT)
	Others: Wegener's, SLE



Special Cases

- Adolescent male with unilateral recurrent epistaxis consider juvenile nasopharyngeal angiofibroma (JNA). This is the most common benign tumour of the nasopharynx
- Thrombocytopenic patients – use resorbable packs to avoid risk of re-bleeding caused by pulling out the removable pack

Investigations

- CBC, PT/PTT (if indicated)
- x-ray, CT as needed

Treatment

- aim is to localize bleeding and achieve hemostasis

1. First-aid

- ABC's
- patient leans forward to minimize swallowing blood
- constant firm pressure applied for 20 min on soft part of nose (not bony pyramid)

2. Assess Blood Loss (can be potentially fatal hemorrhage)

- pulse, blood pressure, and other signs of shock
- IV NS, cross match for 2 units packed RBCs if significant
- IV NS if hypovolemic, or signs of shock

3. Determine Site of Bleeding

- anterior/posterior hemorrhage defined by location in relationship to bony septum
- insert cotton pledget of 4% topical lidocaine ± topical decongestant (i.e. Otrivin), visualize nasal cavity with speculum and aspirate excess blood and clots
- if suspicion of bleeding disorder, coagulation workup

4. Control the Bleeding

- first line topical vasoconstrictors (Otrivin®)
- if first line fails and bleeding adequately visualized, cauterize with silver nitrate
- **do not cauterize both sides of the septum** at one time due to risk of septal perforation from loss of septal blood supply

A. Anterior hemorrhage treatment

- if fail to achieve hemostasis with cauterization:
 - ♦ place anterior pack with half inch Vaseline®-soaked ribbon gauze strips or absorbable packing (i.e. Gelfoam®) layered from nasal floor toward nasal roof extending to posterior choanae for 2 to 3 days
 - ♦ can also attempt packing with Merocel® or nasal tampons of different shapes
 - ♦ can also apply Floseal® (hemostatic matrix consisting topical human thrombin and cross linked gelatin) if other methods fail

B. Posterior hemorrhage treatment

- if unable to visualize bleeding source, then usually posterior source:
 - ♦ place posterior pack using a Foley catheter, gauze pack or Epistat® balloon
 - ♦ subsequently, layer anterior packing bilaterally
 - ♦ antibiotics for any posterior pack or any pack in >48 hours
 - ♦ admit to hospital with packs in for 3 to 5 days
 - ♦ watch for complications: hypoxemia (naso-pulmonic reflex), toxic shock syndrome (Rx: remove packs immediately), pharyngeal fibrosis/stenosis, alar/septal necrosis, aspiration

C. If anterior/posterior packs fail to control epistaxis

- arterial ligation of anterior/posterior ethmoid, branches of internal maxillary, external carotid arteriesselctive embolization of branches of external carotid artery
- ± septoplasty

5. Prevention

- prevent drying of nasal mucosa with humidifiers, saline spray, or topical ointments
- avoidance of irritants
- medical management of hypertension and coagulopathies



If hoarseness present for >2 weeks in a smoker, laryngoscopy must be done to rule out malignancy.
Acute <2 weeks, chronic >2 weeks.

Hoarseness

Definitions

- hoarseness: change in voice quality, ranging from voice harshness to voice weakness reflects abnormalities anywhere along the vocal tract from oral cavity to lungs
- dysphonia: a general alteration in voice quality
- aphonia: no sound emanates from vocal folds

Acute Laryngitis

Etiology

- viral: influenza, adenovirus
- bacterial: Group A *Streptococcus*
- acute voice strain → submucosal hemorrhage → vocal cord edema → hoarseness
- environmental: toxic fume inhalation

Clinical Features

- URTI symptoms, hoarseness, aphonia, cough attacks, ± dyspnea
- true vocal cords erythematous/edematous with vascular injection and normal mobility

Treatment

- usually self-limited, resolves within ~1 week
- voice rest
- humidification
- hydration
- avoid irritants (e.g. smoking)
- treat with antibiotics if there is evidence of coexistent bacterial pharyngitis

**Vocal Cord Paralysis**

Unilateral: affected cord lies in the paramedian position, inadequate glottic closure during phonation → weak, breathy voice.

Bilateral: cords rest in midline therefore voice remains good but respiratory function is compromised and may present as stridor.

Treatment options: voice therapy, injection laryngoplasty (collagen, fat), cord medialization.

**Innervation of Larynx**

Internal branch of superior laryngeal nerve: sensory to larynx above cords.

External branch of superior laryngeal nerve: motor to cricothyroid muscle.

Recurrent laryngeal nerve: all motor to larynx except for cricothyroid muscle; sensory to larynx below cords.

Chronic Laryngitis

Definition

- longstanding inflammatory changes in laryngeal mucosa

Etiology

- repeated attacks of acute laryngitis
- chronic irritants (dust, smoke, chemical fumes)
- chronic voice strain
- chronic sinusitis with postnasal drip (PND)
- chronic alcohol use
- esophageal disorders: GERD, Zenker's diverticulum, hiatus hernia
- systemic: allergy, hypothyroidism, Addison's

Clinical Features

- chronic dysphonia – rule out malignancy
- cough, globus sensation, frequent throat clearing 2° to GERD
- laryngoscopy: cords erythematous, thickened with ulceration/granuloma formation and normal mobility

Treatment

- remove offending irritants
- treat related disorders e.g. antisecretory therapy for GERD
- speech therapy with voice rest
- ± antibiotics, ± steroids to decrease inflammation
- laryngoscopy to rule out malignancy

Vocal Cord Polyps



Definition

- structural manifestation of vocal cord irritation
- acutely, polyp forms 2° to capillary damage in the subepithelial space during extreme voice exertion

Etiology

- most common benign tumour of vocal cords
- voice strain (muscle tension dysphonia)
- laryngeal irritants (GERD, allergies, tobacco)

Epidemiology

- 30 to 50 years of age
- M>F

Clinical Features

- hoarseness, aphonia, cough attacks ± dyspnea
- pedicled or sessile polyp on free edge of vocal cord
- typically polyp asymmetrical, soft and smooth
- more common on the anterior 1/3 of the vocal cord
- polyp are intermittent respiratory distress with large polyps

Treatment

- avoid irritants
- endoscopic laryngeal microsurgical removal if persistent or if high risk of malignancy



Vocal Cords: Polyps vs. Nodules

Polyps	Nodule
Unilateral, asymmetric	Bilateral
Acute onset May resolve spontaneously	Gradual onset Often follow a chronic course
Subepithelial capillary breakage	Acute: submucosal hemorrhage or edema Chronic: hyalinization within submucous lesion
Soft, smooth, fusiform, pedunculated mass	Acute: small, discrete nodules Chronic: hard, white, thickened fibrosed nodules
Surgical excision if persistent or in presence of risk factors for laryngeal cancer	Surgical excision if refractory

Vocal Cord Nodules



Definition

- vocal cord callus
- aka "screamer's or singer's nodules"

Etiology

- early nodules occur 2° to submucosal hemorrhage
- mature nodules result from hyalinization which occurs with long term voice abuse
- chronic voice strain
- URTI, smoke, alcohol

Epidemiology

- frequently in singers, children, bartenders, and school teachers
- F>M

Clinical Features

- hoarseness worst at end of day
- on laryngoscopy:
 - red, soft nodules
 - often bilateral
 - at the junction of the anterior 1/3 and posterior 2/3 of the vocal cords – point of maximal cord vibration
- chronic nodules may become fibrotic, hard, and white

Treatment

- voice rest
- hydration
- speech therapy
- avoid irritants
- surgery rarely indicated for refractory nodules

Benign Laryngeal Papillomas

Etiology

- human papilloma virus (HPV) types 6, 11
- possible hormonal influence, possibly acquired during delivery

Epidemiology

- biphasic distribution – 1) birth to puberty (most common laryngeal tumour) and 2) adulthood

Clinical Features

- hoarseness/"frog voice" and airway obstruction
- can seed into tracheobronchial tree
- highly resistant to complete removal
- some juvenile papillomas resolve spontaneously at puberty
- papillomas in adults may undergo malignant transformation
- laryngoscopy shows wart-like lesions in supraglottic larynx and trachea

Treatment

- CO₂ laser and microsurgery
- adjuvants under investigation: interferon, cidofovir, acyclovir
- Gardasil® HPV vaccine may prevent/decrease the incidence but more research is needed

Laryngeal Carcinoma

- see *Neoplasms of the Head and Neck*, OT34



Salivary Glands

Sialadenitis

Definition

- inflammation of salivary glands

Etiology

- viral most common (mumps)
- bacterial causes: *S. aureus*, *S. pneumoniae*, *H. influenzae*
- obstructive vs. non-obstructive
- obstructive infection involves salivary stasis and bacterial retrograde flow

Predisposing Factors

- HIV
- anorexia/bulimia
- Sjogren's syndrome
- Cushing's, hypothyroidism, DM
- hepatic/renal failure
- meds that increase stasis: diuretics, TCAs, beta-blockers, anticholinergics, antibiotics
- sialolithiasis (can cause chronic sialadenitis)

Clinical Features

- acute onset of pain and edema of parotid or submandibular gland that may lead to marked swelling
- \pm fever
- \pm leukocytosis
- \pm suppurative drainage from punctum of the gland

Investigations

- U/S imaging to differentiate obstructive vs. non-obstructive sialadenitis

Treatment

- bacterial: treat with cloxacillin \pm abscess drainage
- viral: no treatment



Mumps usually presents with bilateral parotid enlargement, \pm sensorineural hearing loss, \pm orchitis.

Sialolithiasis

Definition

- ductal stone (mainly hydroxyapatite) leading to chronic sialadenitis
- 80% in submandibular gland, <20% in parotid gland, ~1% in sublingual gland

Risk Factors

- any condition causing duct stenosis or a change in salivary secretions (e.g. dehydration, diabetes, EtOH, hypercalcemia)

Clinical Features

- pain and tenderness over involved gland
- intermittent swelling related to meals
- digital palpation reveals presence of calculi

Investigations

- sialogram

Treatment

- may resolve spontaneously
- encourage salivation to clear calculus
- remove calculi by dilating duct and orifice or excision through floor of mouth
- if calculus is within the gland parenchyma, then the whole gland must be excised



Bilateral enlargement of the parotid glands may be a manifestation of a systemic disease, such as Sjögren's or an eating disorder (i.e. anorexia, bulimia).

**Management of Sialolithiasis****MASH**

Massage
Analgesia and Antibiotics
Sialogogues (e.g. lemon wedges, sour lemon candies)
Heat (warm compress)

Salivary Gland Neoplasms

Etiology

- anatomic distribution
 - parotid gland: 70 to 85%
 - submandibular gland: 8 to 15%
 - sublingual gland: 1%
 - minor salivary glands, most concentrated in hard palate: 5 to 8%
- malignant (see Table 16 and Table 17)
- benign
 - benign mixed (pleomorphic adenoma): 80%
 - Warthin's tumour (5 to 10% bilateral, M>F): 10%
 - cysts, lymph nodes and adenomas: 10%
 - oncocytoma: <1%

Epidemiology

- 3 to 6% of all head and neck neoplasms in adults
- mean age at presentation: 55 to 65
- M=F



A mass sitting above an imaginary line drawn between the mastoid process and angle of the mandible is a parotid neoplasm until proven otherwise.

Parotid Gland Neoplasms

Clinical Features

- 80% benign (pleomorphic adenoma most common), 20% malignant (mucoepidermoid most common)
- painless slow-growing mass
- if bilateral, suggests benign process (Warthin's tumour, Sjögren's, bulimia, mumps) or possible lymphoma

**DDx Parotid Tumour****Benign**

1. Pleomorphic adenoma
2. Warthin's tumour (more common in men)
3. Cyst

Malignant

1. Mucoepidermoid carcinoma
2. Adenoid cystic carcinoma
3. Acinic cell carcinoma

Investigations

- fine needle aspiration (FNA) biopsy
- CT or MRI to determine extent of tumour

Treatment

- treatment of choice is surgery for all salivary gland neoplasms – benign and malignant
- benign tumours are excised due to risk of malignant transformation
 - pleomorphic adenoma → carcinoma ex-pleomorphic adenoma
- superficial tumour
 - superficial parotidectomy above plane of CN VII, ± radiation
 - incisional biopsy contraindicated
- deep lesion
 - near-total parotidectomy sparing as much of CN VII as possible
 - if CN VII involved then it is removed and cable grafted
- complications of parotid surgery
 - hematoma, infection, salivary fistula, temporary facial paresis, Frey's syndrome (gustatory sweating)

Prognosis

- benign: excellent, <5% of pleomorphic adenomas may recur
- malignant: dependent on stage and type of malignancy (see OT36)



Neck Masses

Approach to a Neck Mass

- ensure that the neck mass is not a normal neck structure (hyoid, transverse process of C1 vertebra)

Table 15. Acquired Causes of Neck Lumps According to Age

Age (yrs)	Possible Causes of Neck Lump
<20	Congenital: lateral (branchial cleft cyst, laryngocele, cystic hygroma), midline (thyroglossal duct cyst) Inflammatory neck nodes (tonsillitis, infectious mononucleosis, Kawasaki's) Lymphoma
20-40	HIV Salivary gland (calculi, infection, tumour) Thyroid (goitre, infection, tumour) Granulomatous disease (TB, sarcoidosis)
>40	Primary or secondary malignant disease

**Zones of Injury to the Neck**

Clavicle → inferior border of cricoid cartilage

- Injuries here have highest mortality
- Angiography, esophagoscopy

Cricoid → angle of mandible

- Most common site, lower mortality due to good accessibility
- To OR for surgical exploration

Angle of mandible → skull base

- Angiography

**Rule of 7s for Duration of Symptoms of a Neck Mass**

- 7 days: inflammatory
- 7 months: neoplastic
- 7 years: congenital

**Inflammatory vs. Neoplastic Neck Masses**

	Inflammatory	Neoplastic
History		
Painful	Y	N
H&N infection	Y	N
Fever	Y	N
Weight loss	N	Y
CA risk factors	N	Y
Age	Younger	Older
Physical		
Tender	Y	N
Rubbery	Y	Occ.
Rock hard	N	Y
Mobile	Y	± fixed
Size	<2 cm	>2 cm

Evaluation

Investigations

- history and physical (including nasopharynx and larynx)
- laboratory investigations
 - WBC – infection vs. lymphoma
 - Mantoux TB test
 - thyroid function tests and scan
- imaging
 - neck U/S
 - CT scan
 - angiography – vascularity and blood supply to mass
 - radiologic exam of stomach, bowel and sinuses
- biopsy – for histologic examination
 - fine needle aspiration (FNA) – least invasive
 - needle biopsy
 - open biopsy – for lymphoma
- identification of primary tumour
 - panendoscopy: nasopharyngoscopy, laryngoscopy, esophagoscopy, bronchoscopy with washings, and biopsy of suspicious lesions
 - biopsy of normal tissue of nasopharynx, tonsils, base of tongue, and hypopharynx
 - primary identified 95% of time → stage and treat
 - primary occult 5% of time – excisional biopsy of node for histologic diagnosis → manage with radiotherapy and/or neck dissection (squamous cell carcinoma)

Congenital Neck Masses in Detail

Branchial Cleft Cysts/Fistulae

Embryology

- at 6th week of development, the 2nd branchial arch grows over the 3rd and 4th arches and fuses with the neighbouring caudal pre-cardial swelling forming the cervical sinus
- 3 types of malformations:
 - branchial fistula – persistent communication between skin and GI tract
 - branchial sinus – blind-ended tract opening to skin
 - branchial cyst – persistent cervical sinus with no external opening

Clinical Features

- 2nd branchial cleft malformations most common
 - fistulas present in infancy as a small opening anterior to the sternocleidomastoid muscle
 - cysts present as a smooth, painless, slowly enlarging lateral neck mass, often following an URTI
- 1st branchial groove malformations present as pre-auricular pit/sinus

Treatment

- surgical removal of cyst or fistula tract
- if infected – allow infection to settle before removal

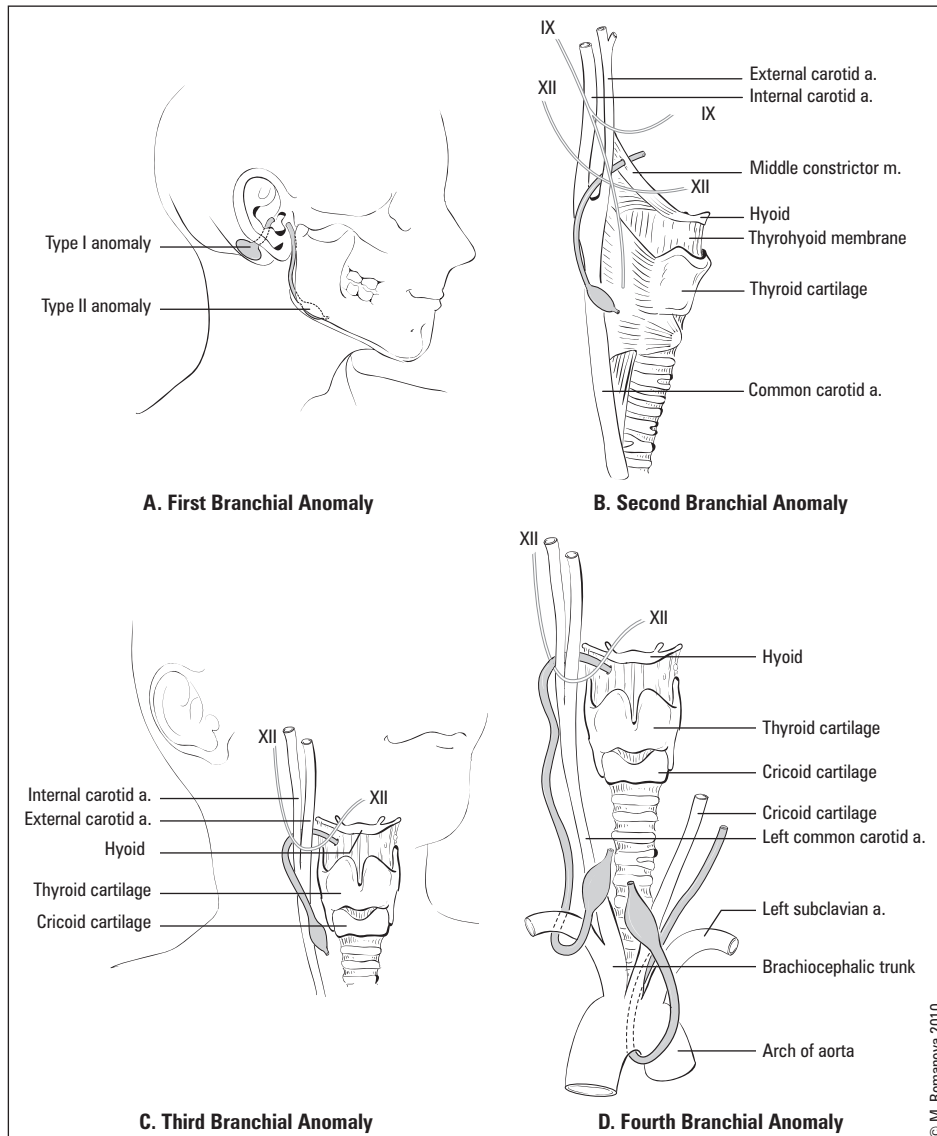


Figure 19. Branchial Cleft Cysts

Thyroglossal Duct Cysts

Embryology

- thyroid originates as ventral midline diverticulum of floor of pharynx caudal to junction of 3rd and 4th branchial arches (foramen cecum)
- thyroid migrates caudally along a tract then curves underneath and down to cricoid
- thyroglossal duct cysts are vestigial remnants of tract

Clinical Features

- usually presents in the 2nd to 4th decades as a midline cyst that elevates with swallowing and tongue protrusion

Treatment

- pre-operative antibiotics to reduce inflammation
- potential for neoplastic transformation so complete excision of cyst and tract up to foramen cecum at base of tongue with removal of central portion of hyoid bone (Sistrunk procedure)

Cystic Hygroma (Lymphangioma)

Definition

- lymphatic malformation arising from vestigial lymph channels of neck

Clinical Features

- usually presents by age 2
- thin-walled cyst extending from floor of mouth to mediastinum, usually in posterior triangle or supraclavicular area
- usually painless, soft, compressible
- infection causes a sudden increase in size

Treatment

- surgical excision if it fails to regress – difficult dissection due to numerous cyst extensions



Neoplasms of the Head and Neck

Pre-Malignant Disease

- leukoplakia
 - hyperkeratosis
 - risk of malignant transformation 5 to 20%
- erythroplakia
 - red superficial patches adjacent to normal mucosa
 - commonly associated with epithelial dysplasia
 - associated with carcinoma in situ or invasive tumour in 40% of cases
- dysplasia
 - histopathologic presence of mitoses and prominent nucleoli
 - involvement of entire mucosal thickness = carcinoma in situ
 - associated progression to invasive cancer in 15 to 30% of cases

Investigations

- initial metastatic screen includes chest x-ray
- scans of liver, brain, and bone only if clinically indicated
- TNM (tumour, nodes, metastases) classification varies slightly depending on the specific type of head and neck tumour (*see online tables*)
- TNM classification widely used for staging in order to:
 - guide treatment
 - indicate prognosis
 - evaluate results of treatment
 - facilitate accurate exchange of information
- CT scan is superior to MRI for the detection of pathologic nodal disease and bone cortex invasion
- MRI is superior to discriminate tumour from mucus and to detect bone marrow invasion
- \pm PET scans

Treatment

- treatment depends on:
 - histologic grade of tumour
 - stage
 - physical and psychological health of patient
 - facilities available
 - expertise and experience of the medical and surgical oncology team



All patients presenting with a head and neck mass should be asked if they are experiencing the following obstructive, referred or local symptoms:

1. Dyspnea or stridor (positional vs. non-positional)
2. Hoarseness or Dysphonia
3. Otalgia
4. Aural fullness
5. Dysphagia



Detection of cervical lymph nodes on physical examination:
False negative rate 15 to 30%
False positive rate 30 to 40%



Pathological lymphadenopathy defined radiographically as:

1. A node > 1.5 cm in diameter
2. A node of any size which contains central necrosis



Common sites of distant metastases for head and neck neoplasms:
lungs > liver > bones

- in general:
 - 1° surgery for malignant oral cavity tumours with radiotherapy reserved for salvage or poor prognostic indicators
 - 1° radiotherapy for nasopharynx, oropharynx, hypopharynx, larynx malignancies with surgery reserved for salvage
 - palliative chemotherapy for metastatic or incurable disease
 - concomitant chemotherapy or alternating chemoradiotherapy may increase survival in resectable/unresectable disease
 - chemotherapy has a role as induction therapy prior to surgery and radiation
 - panendoscopy to detect primary disease when lymph node metastasis is identified
 - anti-EGFR treatment (cetuximab, panitumumab) has a role as concurrent therapy with radiation (for advanced local and regional disease)

Prognosis

- synchronous tumours occur in 9 to 15% of patients
- late development of 2nd primary most common cause of post-treatment failure after 36 months

Table 16. Quick Look-Up Summary of Head and Neck Malignancies – Etiology and Epidemiology

Etiology	Epidemiology	Risk Factors
Oral Cavity		
95% SCC others: sarcoma, melanoma, minor salivary gland tumour	50% on anterior 2/3 of tongue Mean age: 50 to 60 M>F Most common site of H&N cancers	Smoking/EtOH Poor oral hygiene Leukoplakia, erythroplakia UV light – lip Oral HPV infection
Nose and Paranasal Sinus		
75 to 80% SCC then adenoCA and mucoepidermoid 99% in maxillary/ethmoid sinus 10% arise from minor salivary glands	Mean age: 50 to 70 Rare tumours ↓ incidence in last 5 to 10 years	Wood/shoe/textile industry Hardwood dust (nasal/ethmoid sinus) Nickel, chromium (maxillary sinus) Air pollution Chronic sinusitis HPV infection – role unclear
Carcinoma of the Pharynx – Subtypes (Nasopharynx, Oropharynx, Hypopharynx and Larynx)		
Nasopharynx		
90% SCC ~10% lymphoma	Incidence 0.8 per 100,000 100x increased incidence in southern Chinese M:F = 2.4:1 Mean age: 50 to 59	Epstein-Barr virus (EBV) Salted fish Nickel exposure Poor oral hygiene Southern Chinese
Oropharynx		
95% SCC – poorly differentiated	M:F = 4:1 Mean age: 50 to 70	Smoking/EtOH Oral HPV Infection
Hypopharynx		
95% SCC 3 sites: 1. piriform sinus (60%) 2. post-cricoid (30%) 3. post pharyngeal wall (10%)	M>F Mean age: 50 to 70 8 to 10% of all H&N cancer	Smoking/EtOH
Larynx		
SCC most common 3 sites: 1. supraglottic (30 to 35%) 2. glottic (60 to 65%) 3. subglottic (1%)	45% of all H&N cancer M:F = 10:1 Mean age: 45 to 75	Smoking/EtOH Oral HPV Infection
Salivary Gland (see Salivary Gland)		
40% mucoepidermoid 30% adenoid cystic 5% acinic cell 5% malignant mixed 5% lymphoma	Rate of malignancy: Parotid 15 to 25% Submandibular 37 to 43% Minor salivary >80% 3 to 6% of all H&N cancer Mean age: 55 to 65 M=F	
Thyroid (90% benign – 10% malignant)		
60 to 70% papillary 15 to 20% follicular 2 to 5% anaplastic 2 to 5% medullary 1 to 5% Hurthle cell 3% lymphoma 1 to 2% metastatic	Children Adults <30 or >60 Nodules more common in females Malignancy more common in males	Radiation exposure Family history – papillary CA or multiple Endocrine neoplasia – MEN II Older age Male Papillary – Gardner's, Cowden's, familial adenomatous polyposis (FAP)
Parathyroid		
	Rare tumour Mean age: 44 to 55 years	

Access to PET scans across Canada is variable and there are evolving indications regarding its use in the field of head and neck cancer. PET improves diagnosis and treatment of patients with treated thyroid cancer who develop increased serum thyroglobulin without evidence of recurrence on conventional CT/MRI. Additionally, there is likely application in the following clinical circumstances:

- Detection of an unknown primary
- Determining the extent of local disease
- Detection of residual disease after treatment

Source: Cancer Care Ontario. "PET SCAN PRIMER: a guide to the implementation of positron emission tomography imaging in Ontario". Members of the Ontario PET Steering Committee. Date: Aug 31, 2008



Treatment of locoregionally advanced head and neck cancer with concomitant highdose radiotherapy plus cetuximab improves locoregional control and reduces mortality without increasing the common toxic effects associated with radiotherapy to the head and neck.

Bonner JA, et al. Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck. *NEJM* 2006; 354(6):567-578.



Risk Factors for Head and Neck Cancer include:

1. Smoking
2. EtOH (this is synergistic with #1)
3. Radiation
4. Occupational/Environmental exposures
5. Oral HPV infection (independent of smoking and EtOH exposure)



HPV-16 accounts for over 90% of HPV-positive head and neck squamous cell carcinoma.



The smaller the salivary gland the greater the likelihood that a mass in the gland is malignant.

Table 17. Quick Look-Up Summary of Head and Neck Malignancies – Diagnosis and Treatment

Clinical Features	Investigations	Treatment	Prognosis
Oral Cavity			
Asymptomatic neck mass (30%)	Biopsy	1° surgery	5 year: - T1/T2: 75%
Non-healing ulcer ± bleeding	CT	local resection	- T3/T4: 30 to 35%
Dysphagia, sialorrhea, dysphonia		± neck dissection	Poor prognostic indicators:
Oral feter, otalgia leukoplakia or erythroplakia (pre-malignant changes or CIS)		± reconstruction	Depth of invasion, close surgical margins location (tongue worse than floor of mouth)
		2° radiation	Cervical nodes, extra capsular spread
Nose and Paranasal Sinus			
Early symptoms:	CT/MRI	Surgery and radiation	5 year: 30 to 60%
Unilateral nasal obstruction	Biopsy	Chemoradiotherapy for unresectable disease	Poor prognosis 2° to late presentation
Epistaxis, rhinorrhea			
Late symptoms:			
2° to invasion of nose, orbit, nerves, oral cavity, skin, skull base, cribriform plate			
Nasopharynx			
Cervical nodes (60 to 90%)	Nasopharyngoscopy	1° radiation	5 year survival:
Nasal obstruction, epistaxis	Biopsy	2° surgery	- I: 79%
Unilateral AOM ± hearing loss	CT/MRI		- II: 72%
CN III to VI, IX to XII (25%)			- III: 50 to 60%
Proptosis, voice change, dysphagia			- IV: 36 to 42%
Oropharynx			
Odynophagia, otalgia	Biopsy	1° radiation	Base of tongue – control rates
Ulcerated/enlarged tonsil	CT	2° surgery	T1: >90% T4: 13 to 52%
Fixed tongue/trismus/dysarthria		local resection	Tonsils – cure rate
Oral feter, bloody sputum		± neck dissection	T1/T2: 90 to 100% T4: 15 to 33%
Cervical lymphadenopathy (60%)		± reconstruction	HPV-positive tumours have an approximately 20% improved overall survival rate
Distal mets: lung/bone/liver (7%)			
Hypopharynx			
Dysphagia, odynophagia	Pharyngoscopy	1° radiation	T2/T3 cure rate: 60%
Otalgia, hoarseness	Biopsy	2° surgery	T4/5 year survival: 25 to 40%
Cervical lymphadenopathy	CXR r/o lung mets		
	CT		
Larynx			
Dysphagia, odynophagia, globus	Laryngoscopy	1° radiation	5 year T4 >40% (surgery with radiation)
Otalgia, hoarseness,	CT/MRI	2° surgery	Control rate early lesions >90% (radiation)
Dyspnea/stridor		1° surgery for bulky T4	10 to 12% of small lesions fail radiotherapy
Cough/hemoptysis			
Cervical nodes (rare w/ glottic CA)			
Salivary Gland			
Painless mass	Fine needle aspirate	Surgery:	Parotid 10-year survival
CN VII – parotid mass	CT	Benign and malignant	85, 69, 43, and 14% for stages I to IV
Cervical lymphadenopathy		Lymph node sampling	Submandibular
Rapid growth		Post-op radiotherapy	2 year: 82%, 5 year: 69%
Invasion of skin		Chemo if unresectable	Minor salivary gland
Constitutional signs/symptoms			10 year: 83, 52, 25, 23% for stages I to IV
Thyroid			
Thyroid mass, cervical nodes	FNA	1° surgery	Recurrences occur within 5 years
Vocal cord paralysis	U/S	I ¹³¹ for metastatic deposits post-op TSH suppression	Need long-term f/u: clinical exam, thyroglobulin
Hyper/hypothyroidism			
Dysphagia			
Parathyroid			
Increased serum Ca		Wide surgical excision	Recurrence rates: 1-year 27%
Neck mass		Post-op monitoring of serum Ca	5-year 82%
Bone disease, renal disease			10-year 91%
Pancreatitis			Mean survival: 6 to 7 years

Thyroid Carcinoma

Table 18. Cytology results of FNA Samples

Category	Characteristics
Non-diagnostic	
Benign	Macrofollicular or colloid adenomas, chronic autoimmune (Hashimoto's) thyroiditis
Suspicious or indeterminate	Microfollicular or cellular neoplasm
Malignant	



Types of Thyroid Cancer
(from most common to least common)
Papillary
Follicular
Medullary
Anaplastic
Lymphoma

Table 19. Thyroid Carcinoma

	Papillary	Follicular	Medullary	Anaplastic	Lymphoma
Incidence (% of all thyroid cancers)	70 to 75%	10%	3 to 5% (10% familial 90% sporadic)	2 to 5%	<1% 2% of extranodal lymphomas
Route of Spread	Lymphatic	Hematogenous	Lymphatic and hematogenous		
Histology	Orphan Annie nuclei Psammoma bodies	Capsular/blood Vessel invasion Influences prognosis	Amyloid May secrete calcitonin, prostaglandins, ACTH, serotonin, kallikrein or bradykinin	Giant cells Spindle cells	
Other	P's – papillary cancer Popular (most common) Palpable lymph nodes Positive ¹³¹ I uptake Positive prognosis Post-op ¹³¹ I scan to diagnose treatments	F's – follicular cancer Far away mets Female (3:1) NOT FNA (can't be diagnosed by FNA) Favourable prognosis	M's – medullary cancer Multiple endocrine neoplasia (MEN IIa or IIb) aMyloid Median node dissection	More common in elderly 70% in women 20 to 30% have Hx of differentiated thyroid Ca (mostly papillary) or nodular goitres mass Rapidly enlarging neck	Usually non-Hodgkin's Rapidly enlarging goitre Hashimoto's thyroiditis Increased risk 60x 4:1 female predominance dysphagia, dyspnea, stridor, hoarseness, neck pain, facial edema accompanied by "B" symptoms *
Prognosis	98% at 10 years	92% at 10 years	50% at 10 years 20% at 10 years if detected when clinically palpable	20 to 35% at 1 year 13% at 10 years	5 year survival Stage IE 55%-80% Stage IIE 20%-50% Stage IIE/IV 15%-35%
Treatment	Small tumours: Near total thyroidectomy or lobectomy Diffuse/bilateral: Total thyroidectomy Post-op ¹³¹ I tx	Small tumours: Near total thyroidectomy/lobectomy/isthmectomy Large/diffuse tumours: Total thyroidectomy	Total thyroidectomy median lymph node Dissection if lateral cervical nodes +ve modified neck dissection Post-op thyroxine Tracheostomy Screen asymptomatic relatives	Small tumours: Total thyroidectomy ± external beam	Non-surgical Combined radiation Chemotherapy (CHOP**)

*B symptoms = fever, night sweats, weight loss >10% in 6 mos

** CHOP = cyclophosphamide, adriamycin, vincristine, prednisone

Approach to Thyroid Nodule

• Recommendation A:

- all patients with thyroid nodules require evaluation of serum TSH and ultrasound
- any nodule >5 mm with suspicious sonographic features (hypoechoic, microcalcifications, increased nodular vascularity, infiltrative margins, height > width on transverse view) should undergo FNA
- when performing repeat FNA on initially non-diagnostic nodules, US-guided FNA should be employed

• Recommendation B:

- nonpalpable, mostly cystic, or posteriorly located nodules should undergo US-guided FNA as the initial evaluative procedure



A minimum of hemithyroidectomy is required to confirm capsular invasion for diagnosing follicular or Hürthle cell CA.



Indications for post-op radioactive iodine ablation – ¹³¹I

Adjuvant therapy – decrease mortality
RAI therapy – treat persistent cancer

Table 20. Management of the Thyroid Nodule

Treatment	Indications
Radioiodine therapy	Hyperthyroid with suspicious solid mass, that is HOT on thyroid scan
Chemotherapy and / or radiotherapy	Anaplastic CA or thyroid lymphoma
Surgical excision	Recurrent cyst that is "suspicious" on FNA or if patient is extremely anxious Malignancy other than anaplastic CA or thyroid lymphoma Solid "suspicious" mass that is "cold" on thyroid scan (excise to r/o capsular invasion) Hyperthyroid with suspicious solid mass, that is HOT on thyroid scan (hyperfunctioning)

*U/S findings: cystic: risk of malignancy <1%, solid: risk of malignancy approx. 10%, solid with cystic components: risk of malignancy same as if solid



RAI ablation should be offered to patients with distant metastases (M1), gross extrathyroidal extension, primary size >4 cm regardless of patient age (Evidence Grade B and above).

Cooper DS, et al. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2009; 19(11):1167-214.



Pediatric Otolaryngology

Acute Otitis Media (AOM)

Definition

- acute inflammation of middle ear

Epidemiology

- 60 to 70% of children have at least 1 episode of AOM before 3 years of age
- 18 months to 6 years most common age group
- peak incidence January to April
- one third of children have had ≥ 3 or more episodes by age 3

Etiology

- *S. pneumoniae* – 35% of cases (incidence decreasing due to pneumococcus vaccine)
- *H. influenzae* – 25% of cases
- *M. catarrhalis* – 10% of cases
- *S. aureus* and *S. pyogenes* (all beta-lactamase producing)
- anaerobes (newborns)
- Gram-negative enterics (infants)
- viral

Predisposing Factors

- eustachian tube dysfunction/obstruction:
 - swelling of tubal mucosa:
 - ♦ upper respiratory tract infection (URTI)
 - ♦ allergies/allergic rhinitis
 - ♦ chronic sinusitis
 - obstruction/infiltration of eustachian tube ostium:
 - ♦ tumour – nasopharyngeal carcinoma (adults)
 - ♦ adenoid hypertrophy (not due to obstruction but by maintaining a source of infection)
 - ♦ barotrauma (sudden changes in air pressure)
 - inadequate tensor palati function – cleft palate (even after repair)
 - abnormal eustachian tube:
 - ♦ Down syndrome (horizontal position of eustachian tube), Crouzon's, and Apert's syndrome
- disruption of action of:
 - cilia of eustachian tube – Kartagener's syndrome
 - mucus secreting cells
 - capillary network that provides humoral factors, PMNs, phagocytic cells
- immunosuppression/deficiency due to chemotherapy, steroids, diabetes mellitus, hypogammaglobulinemia, cystic fibrosis

Risk Factors

- bottle feeding, pacifier use
- second-hand smoke
- crowded living conditions (day care/group child care facilities) or sick contacts
- male
- family history

Pathogenesis

- obstruction of eustachian tube \rightarrow air absorbed in middle ear \rightarrow negative pressure (an irritant to middle ear mucosa) \rightarrow edema of mucosa with exudate/effusion \rightarrow infection of exudate from nasopharyngeal secretions

Clinical Features

- **triad** of otalgia, fever (especially in younger children), and conductive hearing loss
- rarely tinnitus, vertigo, and/or facial nerve paralysis
- otorrhea if tympanic membrane perforated
- pain over mastoid process
- infants/toddlers
 - ear-tugging
 - hearing loss, balance disturbances (mild)
 - irritable, poor sleeping
 - vomiting and diarrhea
 - anorexia

- otoscopy of tympanic membrane (TM)
 - hyperemia
 - bulging, pus may be seen behind TM
 - loss of landmarks: handle and long process of malleus not visible

Treatment

- antibiotic treatment hastens resolution – 10 day course
 - 1st line:
 - ♦ amoxicillin 80-90 mg/kg/day divided into two doses – safe, effective, and inexpensive
 - ♦ if penicillin allergic: macrolide (clarithromycin, azithromycin), trimethoprim-sulphamethoxazole (Bactrim®)
 - 2nd line (for amoxicillin failures):
 - ♦ double dose of amoxicillin (80 mg/kg/day), amoxicillin-clavulanic acid (Clavulin®)
 - ♦ cephalosporins: cefuroxime axetil (Ceftin®), ceftriaxone IM (Rocephin®), cefaclor (Ceclor®), cefixime (Suprax®)
 - ♦ AOM deemed unresponsive if clinical signs/symptoms and otoscopic findings persist beyond 48 hours of antibiotic treatment
- symptomatic therapy:
 - antipyretics/analgesics (e.g. acetaminophen)
 - decongestants – may relieve nasal congestion but does not treat AOM
- prevention:
 - parent education about risk factors (see above)
 - antibiotic prophylaxis – amoxicillin or macrolide shown effective at half therapeutic dose
 - pneumococcal and influenza vaccine
 - surgery:
 - ♦ choice of surgical therapy for recurrent AOM depends on whether local factors (eustachian tube dysfunction) are responsible (use ventilation tubes), or regional disease factors (tonsillitis, adenoid hypertrophy, sinusitis) are responsible

Antibiotics for Acute Otitis Media in Children

Cochrane Database of Systematic Reviews 2004;1

Study: Meta-analysis of Randomized Controlled Trials (RCTs) on children (>6 mo) with acute otitis media comparing any antibiotic regime to placebo.

Data Sources: Cochrane Central Register of Controlled Trials (2003 issue 1), MEDLINE (January 2000 to March 2003), and EMBASE (January 1990 to March 2003) without language restrictions.

Main Outcomes: 1) Pain at 24 hours, and 2-7 days. 2) Hearing measured by tympanometry at 1 and 3 months.

Patients: Pain: 24 hours, 4 studies (n=717); 2-7 days 9 studies (n=2287). Hearing: 1 month, 3 studies (n=472); 3 months, 2 studies (n=370).

Results: Treatment with antibiotics had no significant impact on pain at 24 hours. However, pain at 2-7 days was lower in the antibiotic groups with an NNT of 16 (p<0.00001). Antibiotics had no significant effect on hearing.

Conclusion: The role of antibiotics is largely restricted to pain control. This can also be achieved by analgesics. Therefore, parents should be counseled that other analgesics may be a safer option.

Indications for Myringotomy and Tympanostomy Tubes in Recurrent AOM and OME (tubes are more commonly inserted for OME, rarely for AOM)

- persistent effusion >3 months (OME)
- lack of response to >3 months of antibiotic therapy (OME)
- persistent effusion for ≥3 months after episode of AOM (OME)
- recurrent episodes of AOM (>7 episodes in 6 months)
- bilateral conductive hearing loss of >20 dB (OME)
- chronic retraction of the tympanic membrane or pars flaccida (OME)
- bilateral OME lasting >4 to 6 mos
- craniofacial anomalies predisposing to middle ear infections (e.g. cleft palate) (OME)
- complications of AOM (see below)

Mclsaac WJ, Coyte PC, Croxford R, Asche CV, Friedberg J, Feldman W. Otolaryngologists' perceptions of the indications for tympanostomy tube insertion in children. *CMAJ*. 162(9):1285-8, 2000 May 2.

Myringotomy and tympanostomy tubes. In: 2000 clinical indicators compendium. Alexandria (VA): American Academy of Otolaryngology-Head and Neck Surgery; 1999.

Complications of AOM

- otologic:
 - TM perforation
 - chronic suppurative OM
 - ossicular necrosis
 - cholesteatoma
 - persistent effusion (often leading to hearing loss)
- CNS:
 - meningitis
 - brain abscess
 - facial nerve paralysis
- other:
 - mastoiditis
 - labyrinthitis
 - sigmoid sinus thrombophlebitis



Complications of Tympanostomy Tubes

Early

- Extrusion
- Blockage
- Persistent otorrhea

Late

- Myringosclerosis
- Persistent TM perforation
- Cholesteatoma

Otitis Media with Effusion (OME)

Definition

- presence of fluid in the middle ear without signs or symptoms of ear infection

Epidemiology

- not exclusively a pediatric disease
- follows AOM frequently in children
- middle ear effusions have been shown to persist following an episode of AOM for 1 mo in 40% of children, 2 mo in 20% and 3+ mo in 10%

Risk Factors

- same as AOM

Clinical Features

- fullness – blocked ear
- hearing loss \pm tinnitus
 - confirm with audiogram and tympanogram (flat) (see Figure 15B and Figure 16B)
- \pm pain, low grade fever
- otoscopy of tympanic membrane:
 - discolouration – amber or dull grey with “glue” ear
 - meniscus fluid level behind TM
 - air bubbles
 - retraction pockets/TM atelectasis
 - most reliable finding with pneumotoscopy is immobility

Treatment

- expectant – 90% resolve by 3 months
- document hearing loss
- no statistical proof that antihistamines, decongestants, antibiotics clear disease faster
- surgery: myringotomy \pm ventilation tubes \pm adenoidectomy (if enlarged)
- ventilation tubes to equalize pressure and drain ear

Complications of Otitis Media with Effusion (OME)

- hearing loss, speech delay, learning problems in young children
- chronic mastoiditis
- ossicular erosion
- cholesteatoma especially when retraction pockets involve pars flaccida or postero-superior TM
- retraction of tympanic membrane, atelectasis, ossicular fixation

Adenoid Hypertrophy

- size peaks at age 5 and resolves by 12 years of age
- increase in size with repeated URTI and allergies

Clinical Features

- nasal obstruction:
 - adenoid facies (open mouth, flat midface, dark circles under eyes)
 - history of hypernasal voice and snoring
 - long term mouth breather; minimal air escape through nose
- choanal obstruction:
 - chronic sinusitis/rhinitis
 - obstructive sleep apnea
- chronic inflammation:
 - nasal discharge, post-nasal drip, and cough
 - cervical lymphadenopathy

Diagnosis

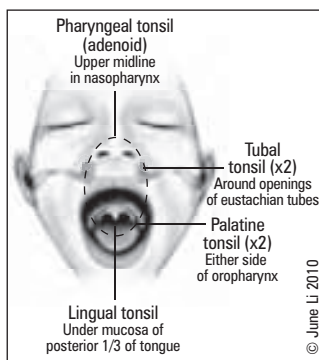
- enlarged adenoids on direct/indirect nasopharyngeal exam
- enlarged adenoid shadow on lateral soft tissue x-ray
- lateral view of the nasopharynx may show a large pad of adenoidal tissue

Complications

- eustachian tube obstruction leading to serous otitis media
- interference with nasal breathing, necessitating mouth-breathing
- malocclusion
- sleep apnea/respiratory disturbance
- orofacial developmental abnormalities

Indications for Adenoidectomy

- chronic upper airway obstruction with sleep disturbance/apnea \pm cor pulmonale
- chronic nasopharyngitis resistant to medical treatment
- chronic serous otitis media and chronic suppurative otitis media (after 2-3 sets of tubes)
- recurrent acute otitis media resistant to antibiotics
- suspicion of nasopharyngeal malignancy
- persistent rhinorrhea

**Figure 20. Waldeyer's Ring**

An interrupted circle of protective lymphoid tissue at the upper ends of the respiratory and alimentary tracts

Contraindications for Adenoidectomy

- bleeding disorders
- recent pharyngeal infection
- short or abnormal palate (cleft or false palate, zona pellucidum)

Complications of Adenoidectomy

- bleeding, infection
- velopharyngeal insufficiency with speech defect \pm nasal regurgitation
- scarring of Eustachian tube orifice

Sleep-Disordered Breathing in Children

Definition

- comprises of a spectrum of sleep-related breathing abnormalities ranging from snoring to obstructive sleep apnea (OSA)

Epidemiology

- peak incidence between 2 and 8 years when tonsils and adenoids are the largest relative to the pharyngeal airway

Etiology

- due to a combination of anatomic and neuromuscular factors:
 - adenotonsillar hypertrophy
 - craniofacial abnormalities
 - neuromuscular hypotonia (i.e. cerebral palsy, Down syndrome)
 - obesity

Clinical Features

- heavy snoring, mouth breathing, pauses or apnea, enuresis, excessive daytime sleepiness, behavioural/learning problems, morning headache, failure to thrive

Investigations

- flexible nasopharyngoscopy for assessment of nasopharynx and adenoids
- polysomnography

Treatment

- surgical management 1st line: adenotonsillectomy
- nonsurgical: behavioural modification, CPAP

Acute Tonsillitis

Etiology

- Group A beta-hemolytic streptococci and Group G streptococci
- *S. pneumoniae*, *S. aureus*, *H. influenzae*, *M. catarrhalis*
- Epstein-Barr virus (EBV)

Clinical Features

- symptoms:
 - sore throat
 - dysphagia, odynophagia, trismus
 - malaise, fever
 - otalgia (referred)
- signs:
 - tender cervical lymphadenopathy especially submandibular, jugulodigastric
 - tonsils enlarged, inflammation \pm exudates/white follicles
 - strawberry tongue, scarletiform rash (scarlet fever)
 - palatal petechiae (infectious mononucleosis)

Investigations

- CBC
- swab for C&S
- latex agglutination tests
- Monospot® – less reliable children <2 years old



Trismus: motor disturbance of the trigeminal nerve, leading to spasm of the muscles of mastication, with difficulty in opening the mouth (lockjaw).



DDx Sore Throat

- Streptococcal pharyngitis
- Viral pharyngitis
- Infectious mononucleosis
- Tonsillitis
- Peritonsillar abscess
- Foreign body/trauma
- Leukemia
- Hodgkin's disease

**Complications of Tonsillitis**

- Rheumatic heart disease
- Arthritis
- Scarlet fever
- Peritonsillar abscess (Quinsy), intratonsillar
- Deep neck space infection
- Sepsis
- Glomerulonephritis

Treatment

- bed rest, soft diet, ample fluid intake
- gargle with warm saline solution
- analgesics and antipyretics
- antibiotics:
 - only after appropriate swab for C&S
 - 1st line penicillin or amoxicillin (erythromycin if penicillin allergy) x 10 days
 - rheumatic fever risk emerges approximately 9 days after the onset of symptoms:
 - ♦ antibiotics are utilized mainly to avoid this serious sequela and to provide earlier symptomatic relief
 - no evidence for the role of antibiotics in the avoidance of post-streptococcal glomerulonephritis
- see sidebar for complications

Peritonsillar Abscess (Quinsy)

Definition

- cellulitis of space behind tonsillar capsule extending onto soft palate leading to abscess

Etiology

- bacterial: Group A strep (GAS) (50% of cases), *S. pyogenes*, *S. aureus*, *H. influenzae*, and anaerobes

Epidemiology

- can develop from acute tonsillitis with infection spreading into plane of tonsillar bed
- unilateral
- most common in 15 to 30 year old age group

Clinical Features

- fever and dehydration
- sore throat, dysphagia and odynophagia
- extensive peritonsillar swelling but tonsil may appear normal
- edema of soft palate
- uvular deviation
- involvement of motor branch of CN V → can lead to increased salivation and trismus
- dysphonia with “hot potato” voice (edema → failure to elevate palate) 2° to CN X involvement
- unilateral referred otalgia
- cervical lymphadenitis

Complications

- aspiration pneumonia 2° to spontaneous rupture of abscess
- airway obstruction
- lateral dissection into parapharyngeal and/or carotid space
- bacteremia
- retropharyngeal abscess

Treatment

- secure airway
- surgical drainage (incision or needle aspiration) with C&S
- warm saline irrigation
- IV penicillin G x 10 days if cultures positive for GAS
- add oral/IV metronidazole or clindamycin x 10 days if culture +ve for *Bacteroides*
- possible tonsillectomy 6 weeks later with interim oral antibiotic prophylaxis for high risk individuals

Other Parapharyngeal Space Infection

- pharyngitis
- parotitis (see *Salivary Gland*, OT30)
- otitis
- mastoiditis (Bezold's abscess)
- odontogenic infection

**Quinsy Triad**

- Trismus
- Uvular deviation
- Hot potato voice

Tonsillectomy

Absolute Indications

- acute airway obstruction \pm cor pulmonale
- suspected malignancy, especially if unilateral tonsillar hypertrophy (lymphoma/squamous cell carcinoma or an unusual infection such as *Mycobacterium tuberculosis*, atypical mycobacteria, fungal organism or actinomycosis)
- acute hemorrhage (rare)

Relative Indications

- age 1 to 4 years: tonsillar hypertrophy leading to:
 - sleep apnea \rightarrow cor pulmonale
 - chronic nasal obstruction or mouth breathing \rightarrow malocclusion
 - difficulty swallowing \rightarrow FTT
 - speech abnormalities
 - severe orofacial/dental abnormalities
 - tonsilolithiasis (small cylindrical calcific inclusions within the tonsillar crypts)
 - recurrent/chronic otitis media
- school age: chronic recurrent tonsillitis if 4-7 episodes in 1 year, >5 episodes/year over 2 consecutive years or >3 episodes/year over 3 consecutive years
- any complication of tonsillitis:
 - quinsy, parapharyngeal abscess, retropharyngeal abscess
 - strep bacteremia: rheumatic heart disease, nephritis, arthritis

Relative Contraindications

- repaired cleft palate
- hemophilia
- epidermolysis bullosa
- retrognathia

Airway Problems in Children

DIFFERENTIAL DIAGNOSIS BY AGE GROUP

Neonates (obligate nose breathers)

- extralaryngeal:
 - choanal atresia (e.g. CHARGE syndrome)
 - nasopharyngeal dermoid, glioma, encephalocele
 - glossoptosis – Pierre-Robin sequence, Down syndrome, lymphangioma, hemangioma
- laryngeal:
 - laryngomalacia – most common cause of stridor in children
 - laryngocele
 - vocal cord palsy (Arnold-Chiari malformations)
 - glottic web
 - subglottic stenosis
 - laryngeal cleft
- tracheal:
 - tracheoesophageal fistula
 - tracheomalacia
 - vascular rings

2 to 3 Months

- congenital:
 - laryngomalacia
 - vascular: subglottic hemangioma (more common), innominate artery compression, double aortic arch
 - laryngeal papilloma
- acquired:
 - subglottic stenosis – post intubation
 - tracheal granulation – post intubation
 - tracheomalacia – post tracheotomy and tracheoesophageal fistula (TEF) repair

Infants – Sudden Onset

- foreign body aspiration
- croup
- bacterial tracheitis
- caustic ingestion
- epiglottitis

Children and Adults

- infection:
 - Ludwig's angina
 - peritonsillar-parapharyngeal abscess
 - retropharyngeal abscess
- neoplastic:
 - squamous cell carcinoma (SCC) (adults): larynx, hypopharynx
 - retropharyngeal: lymphoma, neuroblastoma
 - nasopharyngeal: carcinoma, rhabdomyosarcoma
- allergic:
 - angioneurotic edema
 - polyps (suspect cystic fibrosis in children)
- trauma:
 - laryngeal fracture, facial fracture
 - burns and lacerations
 - post-intubation
 - caustic ingestion
- congenital:
 - lingual thyroid/tonsil

Signs of Airway Obstruction

Stridor

- note quality, timing
- body position important:
 - lying prone: subglottic hemangioma, double aortic arch
 - lying supine: laryngomalacia, glossoptosis
- site of stenosis:
 - vocal cords or above: inspiratory stridor
 - subglottis and extrathoracic trachea: biphasic stridor
 - distal tracheobronchial tree: expiratory stridor

Respiratory Distress

- nasal flaring
- supraclavicular and intercostal indrawing
- sternal retractions
- use of accessory muscles of respiration
- tachypnea
- cyanosis
- altered LOC

Feeding Difficulty and Aspiration

- supraglottic lesion
- laryngomalacia
- vocal cord paralysis
- post laryngeal cleft → aspiration pneumonia
- tracheoesophageal fistula

Acute Laryngotracheobronchitis (Croup)

- inflammation of tissues in subglottic space ± tracheobronchial tree
- swelling of mucosal lining and associated with thick, viscous, mucopurulent exudate which compromises upper airway (subglottic space narrowest portion of upper airway)
- normal function of ciliated mucous membrane impaired

Etiology

- viral: parainfluenzae I (most common), II, III, influenza A and B, RSV



Symptoms and signs of airway obstruction require a full assessment to diagnose potentially serious causes.



Signs of Croup – the 3 S's
 Stridor
 Subglottic swelling
 Seal bark cough

Clinical Features

- age 4 months to 5 years
- preceded by URTI symptoms
- generally occurs at night
- biphasic stridor and croupy cough (loud, sea-lion bark)
- appear less toxic than epiglottitis
- supraglottic area normal
- rule out foreign body and subglottic stenosis
- “steeple-sign” on AP x-ray of neck
- if recurrent croup, think subglottic stenosis

Treatment

- racemic epinephrine via nebulizer q1 to 2h, prn
- systemic corticosteroids (e.g. dexamethasone, prednisone)
- adequate hydration
- close observation for 3 to 4 hours
- intubation if severe
- hospitalize if poor response to steroids after 4 hours and persistent stridor at rest
- consider alternate diagnosis if poor response to therapy (e.g. bacterial tracheitis)

Acute Epiglottitis

- acute inflammation causing swelling of supraglottic structures of the larynx without involvement of vocal cords

Etiology

- *H. influenzae* type B
- relatively uncommon condition due to HiB vaccine

Clinical Features

- any age, most commonly 1 to 4 years
- rapid onset
- toxic-looking, fever, anorexia, restlessness
- cyanotic/pale, inspiratory stridor, slow breathing, lungs clear with decreased air entry
- prefers sitting up, open mouth, drooling, tongue protruding, sore throat, dysphagia

Investigations and Management

- investigations and physical examination may lead to complete obstruction, thus preparations for intubation or tracheotomy must be made prior to any manipulation
- stat ENT/anesthesia consult(s)
- lateral neck radiograph – cherry-shaped epiglottic swelling (“thumb sign”) – only if stable
- WBC (elevated), blood and pharyngeal cultures after intubation

Treatment

- secure airway
- IV access with hydration
- antibiotics – IV cefuroxime, cefotaxime, or ceftriaxone
- moist air
- extubate when leak around tube occurs and afebrile
- watch for meningitis



When managing epiglottitis, it is important not to agitate the child, as this may precipitate complete obstruction.

Subglottic Stenosis

Congenital

- diameter of subglottis <4 mm in neonate (due to thickening of soft tissue of subglottic space or maldevelopment of cricoid cartilage)

Acquired

- following nasotracheal intubation due to:
 - long duration
 - trauma of intubation
 - large tube size
 - infection

Clinical Features

- biphasic stridor
- respiratory distress
- recurrent/prolonged croup

Diagnosis

- laryngoscopy
- CT



Acquired subglottic stenosis is now rare due to the use of smaller, softer tubes and secure taping to prevent movement.

Treatment

- if soft tissue – laser and steroids
- if cartilage – laryngotracheoplasty (LTP)
- balloon dilatation

Laryngomalacia

- elongated omega-shaped epiglottis, short aryepiglottic fold, pendulous mucosa
- caused by indrawing of supraglottis on inspiration

Clinical Features

- high-pitched crowing inspiratory stridor at 1 to 2 weeks
- constant or intermittent and more pronounced supine
- usually mild but when severe can be associated with feeding difficulties, leading to failure to thrive

Treatment

- observation is usually sufficient as symptoms spontaneously subside by 12 to 18 months in >90% of cases
- in the case of severe laryngomalacia, division of the aryepiglottic folds provides relief

Foreign Body**Ingested**

- usually stuck at cricopharyngeus
- coins, toys
- presents with drooling, dysphagia, stridor if very large

Aspirated

- usually stuck at right mainstem bronchus
- peanuts, carrot, apple core, popcorn, balloons
- presentation
 - stridor if lodged in trachea
 - unilateral “asthma” if bronchial, therefore often misdiagnosed as asthma
 - if impacts to totally occlude airway: cough, lobar pneumonia, atelectasis, mediastinal shift, pneumothorax

Diagnosis and Treatment

- inspiration-expiration chest x-ray (if patient is stable)
- bronchoscopy and esophagoscopy with removal
- rapid onset, not necessarily febrile or elevated WBC

Deep Neck Space Infection

- most commonly arise from an infection of the mandibular teeth, tonsils, parotid gland, deep cervical lymph nodes, middle ear, or the sinuses
- often a rapid onset and may progress to fatal complications

Etiology

- usually mixed aerobic and anaerobes that represent the flora of the oral cavity, upper respiratory tract, and certain parts of the ears and eyes

Clinical Features

- sore throat or pain and trismus
- dysphagia and odynophagia
- stridor and dyspnea
- late findings may include dysphonia and hoarseness
- swelling of the face and neck, erythema
- asymmetry of the oropharynx with purulent oral discharge
- lymphadenopathy

Diagnosis

- lateral cervical view of the plain radiograph
- CT
- MRI

Treatment

- secure the airway
- surgical drainage
- maximum doses of IV systemic antimicrobials regimens according to the site of infection



Laryngomalacia is the most common cause of stridor in infants.



Foreign body inhalation is the most common cause of accidental death in children.



Batteries MUST be ruled out as a foreign body (vs. coins) as they are lethal and can erode into the aorta.



Trismus means the pterygoids are involved and airway will become increasingly hard to access.



These investigations should be obtained carefully and the surgeon should consider accompanying the patient for the x-ray as the worst place to lose an airway is during imaging.



Ludwig's angina is the prototypical infection of the submandibular and sublingual space.



In Ludwig's angina, the floor of mouth feels hard on palpation.

Common Medications

Table 21. Antibiotics

Generic Name (Brand Name)	Dosing Schedule	Indications	Comments
amoxicillin (Amoxil [®] , Amoxi [®] , Amox [®])	Adult: 500 mg PO tid Children: 80-90 mg/kg/day in 2 divided doses	<i>Streptococcus</i> , <i>Pneumococcus</i> , <i>H. influenzae</i> , Proteus coverage	In patients with infectious mononucleosis, may cause rash
piperacillin with tazobactam (Zosyn [®])	3 g PO q6h	Gram-positive and negative aerobes and anaerobes plus <i>Pseudomonas</i> coverage	May cause pseudomembranous colitis
ciprofloxacin (Cipro [®] , Ciloxan [®])	500 mg PO bid	<i>Pseudomonas</i> , <i>Streptococci</i> , MRSA, and most Gram-negative; no anaerobic coverage	Do not give quinolones to children
erythromycin (Erythrocin [®] , EryPed [®] , Staticin [®] , T-Stat [®] , Erybid [®] , Novorythro Encap [®])	500 mg PO qid	Alternative to penicillin	Ototoxic

Table 22. Otic Drops

Generic Name (Brand Name)	Dose	Indications / Notes
ciprofloxacin (Ciprodex [®])	4 gtt in affected ear bid	For otitis externa and complications of otitis media <i>Pseudomonas</i> , <i>Streptococci</i> , MRSA, and most Gram-negative; no anaerobic coverage
neomycin, polymyxin B sulfate, and hydrocortisone (Cortisporin Otic [®])	5 gtt in affected ear tid	For otitis externa Used for inflammatory conditions which are currently infected or at risk of bacterial infections May cause hearing loss if placed in inner ear
hydrocortisone and acetic acid (VoSol HC [®])	5-10 gtt in affected ear tid	Bactericidal by lowering pH
tobramycin and dexamethasone (TobraDex [®])	5-10 gtt in affected ear bid	For chronic suppurative otitis media Risk of vestibular or cochlear toxicity

Table 23. Nasal Sprays

Generic Name (Brand Name)	Indications	Notes: General
Steroid		
flunisolide (Rhinalar [®])	Allergic rhinitis	Requires up to four weeks of consistent use to have effect
budesonide (Rhinocort [®])	Chronic sinusitis	Long term use
triamcinolone (Nasacort [®])		Dries nasal mucosa; get minor bleeding
beclomethasone (Beconase [®])		Patient should stop if epistaxis
mometasone furoate, monohydrate (Nasonex [®])		May sting
fluticasone furoate (Avamys [®])		Flonase [®] and Nasonex [®] not absorbed systemically
Antihistamine		
levocarbastine (Livostin [®])	Allergic rhinitis	Immediate effect If no effect by 3 days then discontinue Use during allergy season
Decongestant		
xylometazoline (Otrivin [®])	Acute sinusitis	Careful if patient has hypertension
oxymetazoline (Dristan [®])	Rhinitis	Short term use (<5 days)
phenylephrine (Neosynephrine [®])		If long term use, can cause decongestant addiction (i.e. rhinitis medicamentosa)
Antibiotic/Decongestant		
framycetin, gramicidin, phenylephrine (Soframycin [®])	Acute sinusitis	
Anticholinergic		
ipratropium bromide (Atrovent [®])	Vasomotor rhinitis	Careful not to spray into eyes Increased rate of epistaxis when combined with topical nasal steroids
Lubricants		
saline, NeilMed [®] , Rhinaris [®] , Secaris [®] , Polysporin [®] , Vaseline [®]	Dry nasal mucosa	Use pm Rhinaris [®] and Secaris [®] may cause stinging

Source: Dr. M.M. Carr icarus.med.utoronto.ca/carr/manual/sprays.html

References

Textbooks

- Bailey BJ. Head and Neck Surgery-Otolaryngology. 2nd ed. Philadelphia. Lippincott Williams and Wilkins. 1998.
- Becker W, Naumann HH, Pfaltz CR. Ear, Nose, and Throat Diseases. 2nd ed. New York. Thieme Medical Publishers. 1994.
- Dhillon RS, East CA. Ear, Nose, and Throat, and Head and Neck Surgery: an illustrated colour text. 2nd ed. New York. Churchill & Livingston. 1999. p122.
- Jafek BW, Murrow BW. ENT Secrets. 2nd ed. Philadelphia. Hanley & Belfus. 2001. p608.
- Lee KJ (ed). Essential Otolaryngology: Head and Neck Surgery. 8th ed. McGraw-Hill. New York. 2003. p1136.
- Lucente FE, Har-El G. (eds). Essentials of Otolaryngology. 4th ed. Philadelphia. Lippincott Williams and Wilkins. 1999. p488.
- Layland MK (ed). Washington manual otolaryngology survival guide. Philadelphia. Lippincott Williams and Wilkins. 2003. p187.
- Pasha R. Otolaryngology Head and Neck Surgery Clinical Reference Guide. 2nd ed. San Diego. Plural Publishing. 2006.

Journal Articles

- Berman S. Current Concepts: Otitis Media in Children. NEJM. 1995; 332(23): 1560-1565.
- Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck. NEJM. 2006; 354:567-578.
- Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2009; 19:1167-1214.
- D'Souza G, Kreimer AR, Viscidi R, et al. Case-Control Study of Human Papillomavirus and Oropharyngeal Cancer. NEJM. 2007; 356:1944-56.
- Fakhry C, Westra WH, Li S, et al. Improved Survival of Patients with Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma in a Prospective Clinical Trial. J Natl Cancer Inst. 2008; 100:261-9.
- Forastiere A, Koch W, Trotti A, Sidransky D. Head and Neck Cancer. NEJM. 2001; 345: 1890-1900.
- Furman JM, Cass SP. Benign Paroxysmal Positional Vertigo. NEJM. 1999; 341:1590-1596.
- Hilton M, Pinder D. The Epley (canalith repositioning) maneuver for benign paroxysmal positional vertigo. Cochrane Ear, Nose, and Throat Disorders Group. Cochrane Database of Systematic Reviews. 2004; Issue 4.
- Jackson CG, von Doersten PG. The Facial Nerve: Current Trends in Diagnosis, Treatment, and Rehabilitation. Otolaryngology for the Internist. 1999; 83:179-195.
- Low DE, Desrosiers M, McSherry J, et al. A practical guide for the diagnosis and treatment of acute sinusitis. CMAJ. 1997; 156:S1-14.
- MacCallum PL, Parnes LS, Sharpe MD, Harris C. Comparison of open, percutaneous and translaryngeal tracheostomies. Otolaryngology Head Neck Surgery. 2000; 122:686-690.
- McIsaac WJ, Coyte PC, Croxford R, et al. Otolaryngologists' perceptions of the indications for tympanostomy tube insertion in children. CMAJ. 2000; 162:1285-1288.
- Strafford ND, Wilde A. Parotid Cancer. Surgical Oncology. 1997; 6:209-213.

Rachel Markin, Babak Rashidi, Tamar Rubin and Elizabeth Yeboah, chapter editors

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Pediatric Quick Reference Values

Table 1. Average Vitals at Various Ages

Age	Pulse (bpm)	Resp. Rate (br/min)	sBP (mmHg)
Neonate	90 – 170	40 – 60	70 – 90
3-12 months	80 – 165	30 – 55	80 – 100
1-2 years	80 – 125	25 – 45	90 – 100
3-11 years	70 – 115	18 – 30	100 – 110
12-15 years	60 – 100	12 – 18	110 – 130

Primary Care Pediatrics

Regular Visits

- usual schedule: newborn, within 1 week post-discharge, 1, 2, 4, 6, 9, 12, 15, 18, 24 months
 - yearly until age 6, then every other year until yearly again after age 11
- history
- physical exam
- immunization (see *Immunization*, P4)
- counselling/anticipatory guidance (see *Nutrition* P6, *Colic* P10, *Sudden Infant Death Syndrome (SIDS)* P11, and *Injury Prevention Counselling* P11 sections)

Developmental Milestones

Table 2. Developmental Milestones

Age	Gross Motor	Fine Motor	Speech and Language	Adaptive and Social Skills
6 weeks	Prone: lifts chin intermittently	—	—	Social smile
2 months	Prone: arms extended forward	Pulls at clothes	Coos	Recognizes parents
4 months	Prone: raises head + chest, rolls over, no head lag	Reach and grasp, objects to mouth	Responds to voice, laughs	
6 months	Prone: weight on hands, tripod sit	Ulnar grasp, transfers objects from hand to hand	Begins to babble, responds to name	Stranger anxiety beginning of object permanence
9 months	Pulls to stand, crawls	Finger-thumb grasp	"Mama, dada" – appropriate, imitates 1 word	Plays games, plays peek-a-boo, separation/stranger anxiety
12 months	Walks with support	Pincer grasp, throws	2 words, follows 1-step command	Drinks with cup, waves bye-bye
15 months	Walks without support	Draws a line	Jargon	Points to needs
18 months	Climbs up steps with help	Tower of 3 cubes, scribbling	10 words, follows simple commands	Uses spoon, points to body parts
24 months	Climbs up 2 feet/step, runs, kicks ball, walks up and down steps	Tower of 6 cubes, undresses	2-3 word phrases, uses "I, me, you", 50% intelligible	Parallel play, helps to dress
3 years	Tricycle, climbs up 1 foot/step, down 2 feet/step, stands on one foot, jumps	Copies a circle and a cross, puts on shoes	Prepositions, plurals, counts to 10, 75% intelligible	Dress/undress fully except buttons, knows sex, age
4 years	Hops on 1 foot, down 1 foot/step	Copies a square, uses scissors	Tells story, knows 4 colours, speech intelligible, uses past tense	Cooperative play, toilet trained, buttons clothes, knows names of body parts
5 years	Skips, rides bicycle	Copies a triangle, prints name, ties shoelaces	Fluent speech, future tense, alphabet	



Pediatric Developmental Milestones

- 1 year:**
- Single words
- 2 years:**
- 2 word sentences
 - Understands 2 step commands
- 3 years:**
- 3 word combos
 - Repeats 3 numbers
 - Rides tricycle
- 4 years:**
- Draws square
 - Counts 4 objects



Developmental Red Flags

- Gross motor:** Not walking at 18 mos
- Fine motor:** Handedness at <10 mos
- Speech:** <3 words at 18 mos
- Social:** Not smiling at 3 mos
- Cognitive:** No peek-a-boo at 9 mos



Reflexes

- **Rooting reflex:** infant pursues tactile stimuli near the mouth
- **Parachute reflex:** tilting the infant to the side while in a sitting position results in ipsilateral arm extension (appears by 6-8 months)
- **Upgoing plantar reflexes (Babinski sign):** is normal in infants (i.e. <2 yrs)

Primitive Reflexes

- reflexes seen in normal newborns
- may indicate abnormality (e.g. cerebral palsy) if persist after 4-6 months
- Moro reflex
 - infant is placed semi-upright, head supported by examiner's hand, sudden withdrawal of supported head with immediate resupport elicits reflex
 - reflex consists of abduction and extension of the arms, opening of the hands, followed by flexion and adduction of arms
 - absence of Moro suggests CNS injury; asymmetry suggests focal motor lesions (e.g. brachial plexus injury)
- Galant reflex
 - infant is held in ventral suspension and one side of the back is stroked along paravertebral line; the pelvis will move in the direction of stimulated side
- grasp reflex: flexion of infant's fingers with the placement of a finger in the infant's palm
- asymmetric tonic neck reflex: turning the head results in the "fencing" posture (extension of ipsilateral leg and arm and flexion of contralateral leg)
- placing and stepping reflex ("primitive walking"): infant places foot on a surface when it is brought into contact with it



Routine Immunization

Table 3. Routine Immunization Schedule

Vaccine	Schedule	Route	Reaction	Contraindications
DTaP-IPV	2, 4, 6, 18 mos 4-6 yrs	IM	At 24-48 hrs Minor: fever, local redness, swelling, irritability Major: prolonged crying (1%), hypotonic unresponsive state (1:1750), seizure (1:1950) on day of vaccine Prophylaxis: acetaminophen 10-15 mg/kg given 4 hrs prior to injection and q4h afterwards	Previous anaphylactic reaction to vaccine, evolving unstable neurologic disease, hyporesponsive/hypotonic following previous vaccine, anaphylactic reaction to neomycin or streptomycin
Hib	2, 4, 6, 18 mos	IM	Minor: fever, local redness, swelling, irritability	
Pneu-C	2, 4, 6, 15 mos	IM	Minor: fever, local redness, swelling, irritability	
MMR*	12, 18 mos	SC	At 7-14 days Fever, measles-like rash, lymphadenopathy, arthralgia, arthritis, parotitis (rare)	Pregnancy, immunocompromised infants (except healthy HIV positive children), anaphylactic reaction to gelatin
Men-C	2, 4, 6 mos OR 12 mos	IM	Redness/swelling (<50%), fever (9%), irritability (<80%), rash (0.1%)	
Var*	15 mos	SC	Mild local reaction (20% but higher in immunocompromised) Mild varicella-like papules or vesicles (5%) Low-grade fever (15%)	Pregnant or planning to get pregnant within next 3 months, anaphylactic reaction to gelatin
Hep B	3 doses: 0, 1, 6 mos; given in some provinces in grade 7 (given at birth if at increased risk i.e. from endemic country, given with HBIG if mother HBsAg +ve)	IM	Local redness, swelling	Anaphylactic reaction to Baker's yeast
dTap	Start at 14-16 yrs	IM	Anaphylaxis (very rare)	Pregnancy (1st trimester)
Td	Adult yrs, q10 yrs	IM	Local erythema and swelling (70%)	
Flu**	Start as 6-23 mos, every autumn	IM	Local tenderness at injection site, fever, malaise, myalgia, rash, febrile seizures Hypersensitivity reactions	Anaphylactic reaction to eggs, <6 mos of age



Safety of MMR Vaccine

According to the CDC, the weight of currently available scientific evidence does not support the hypothesis that MMR vaccine causes either autism or IBD.

The landmark paper linking autism to the MMR vaccine (*Lancet* 1998; 351(9103):637-41) was retracted due to false claims in the article (*Lancet* 2010; 375(9713):445).

Table 3. Routine Immunization Schedule (continued)

Vaccine	Schedule	Route	Reaction	Contraindications
HPV	3 doses: 0, 2, 6 mos for females between 9-26 Given in some provinces in grade 7 or 8	IM	Local tenderness, redness, itching, swelling at injection site, fever	

DTaP-IPV – diphtheria, tetanus, acellular pertussis, inactivated polio vaccine (for children under 7 yrs)

MMR – measles, mumps, rubella vaccine Pneu-C – pneumococcal 7-valent conjugate vaccine

Hib – Hemophilus influenzae type b conjugate vaccine Var – varicella vaccine

Men-C – meningococcal C conjugate vaccine dTap – diphtheria, tetanus, acellular pertussis vaccine (adolescent/adult formulation)

Hep B – Hepatitis B vaccine Td – tetanus and diphtheria adult type formulation

Flu – influenza vaccine HPV – human papilloma virus vaccine

*If varicella vaccine and MMR vaccine not given during the same visit, they must be administered at least 28 days apart.

**For children with severe or chronic disease, e.g. cardiac disease, pulmonary disease, renal disease, sickle cell disease, diabetes, endocrine disorders, HIV, immunosuppressed, long-term aspirin therapy, or those who visit residents of chronic care facilities

Adapted from: National Advisory Committee on Immunization. *Recommended Immunization Schedule for Infants, Children and Youth* (updated March 2005)

Administration of Vaccines

- injection site
 - infants (<12 months old): anterolateral thigh
 - children: deltoid
- DTaP+IPV+Hib (Pentacel®, Pentavax®): 5 vaccines given as one IM injection
- two live vaccines (varicella, MMR) must be given subcutaneously either at the same visit or separated by 4 weeks or more

Contraindications to Any Vaccine

- moderate to severe illness ± fever (no need to delay vaccination for mild URTI)
- allergy to vaccine component

Possible Adverse Reactions

- any vaccine
 - local: induration or tenderness (MMR is especially painful!)
 - systemic: fever, rash
 - allergic: urticaria, rhinitis, anaphylaxis
- specific vaccine reactions (see Table 3)

Other Vaccines

Hepatitis A

- inactivated monovalent hepatitis A vaccine (Havrix®, Vaqta®, Avaxim®, Epaxal Berna®)
- given as a series of 2 vaccinations 4-6 months apart
- recommended as pre-exposure prophylaxis for individuals at increased risk of infection (travel to endemic countries, residents of communities with high endemic rates, IV drug use)
- can also be given as a combination vaccine with Hep B (Twinrix®)
- immunoglobulin can be used for short-term protection in infants and immunocompromised patients

BCG Vaccine

- infants of parents with infectious TB at time of delivery
- groups/communities with high rates of disease/infection (offered to aboriginal children on reserves), health care workers at risk
- only given if patient has a negative TB skin test
- side effects: erythema, papule formation 3-6 weeks after intradermal injection, enlargement of regional lymph nodes

TB Skin Test (Mantoux)

- screen high risk populations only (family history, HIV, immigrants from countries with increased incidence, substance abuse in family, homeless, aboriginal)
- intradermal injection of tuberculous antigen, read result at 48-72 hrs
- TB test should be postponed for 4-6 weeks after administration of live BCG vaccine due to risk of false positive result
- test interpretation
 - check area of raised INDURATION (not just area of erythema) at 48-72 hours
 - positive result if:
 - ♦ >15 mm: children >4 years with no risk factors
 - ♦ >10 mm: children <4 years, or at risk for environmental exposure
 - ♦ >5 mm: children with close TB contact, immunosuppressed
- BCG history irrelevant – does not usually give positive response (unless <6 weeks previously)
- positive reaction means active disease or previous contact with TB

Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis
NEJM 2006; 354:11-22
Study: Randomized, double-blind, phase 3 trial.
Patients: 63,225 healthy infants from Latin America and Finland.
Intervention: Two oral doses of HRV vaccine vs. placebo at 2 and 4 mos of age.
Outcome: Episodes of gastroenteritis and severity
Results: The vaccine is 85% efficacious against severe rotavirus gastroenteritis and hospitalizations associated with gastroenteritis and 100% efficacious against more severe gastroenteritis.



Quadrivalent Meningococcal Vaccine (Menactra®)

- given in some provinces in Grade 9
- protects against *Neisseria meningitidis* strains A, C, W-135, and Y
- in Canada, currently recommended for patients with asplenia, travelers to endemic areas (such as the Hajj in Mecca), laboratory workers, and military recruits

Rotavirus Vaccine (RotaTeq®)

- oral vaccine given in 3 doses with first at age 6-12 weeks
- shown to reduce viral gastroenteritis in infants
- not currently covered in Canada

Nutrition

Breastfeeding

- colostrum for first few days = clear fluid with nutrients (high protein, low fat) and immunoglobulins
- full milk production by 3-7 days; mature milk by 15-45 days
- support for mothers who want to breast feed should start while in hospital
- signs of inadequate intake: <6 wet diapers per day after first week, sleepy or lethargic, <7 feeds per day, sleeping throughout the night <6 weeks, weight loss >10% of birth weight, jaundice
 - rule of thumb: ~1 stool/day of age for first week
- feeding schedule (newborn baby needs 120 kcal/kg/day)
 - premature infants: q2-3 hours
 - term infants: q3.5-4 hours, q5 hours at night until about 2-3 months of age
- breast-fed babies require the following supplements
 - vitamin K (given IM at birth)
 - vitamin D (Ddrops®) 400 IU/day, 800 IU/day in northern communities
 - fluoride (after 6 months if not sufficient in water supply)
 - iron: from 4 months to 12 months (iron fortified cereals or ferrous sulphate solution)

Contraindications to Breastfeeding

- mother receiving chemotherapy or radioactive compounds
- mother with HIV/AIDS, active untreated TB, herpes in breast region
- mother using >0.5 g/kg/day alcohol and/or illicit drugs (decrease milk production and/or directly toxic to baby)
- mother taking certain medications e.g. antimetabolites, bromocriptine, chloramphenicol, high dose diazepam, ergots, gold, metronidazole, tetracycline, lithium, cyclophosphamide
- Note: oral contraceptive pills (OCP) not a contraindication to breastfeeding (estrogen may decrease lactation but is not dangerous to infant)

Advantages of Breastfeeding

- "Breast is Best" – exclusive breastfeeding during the first 4 months of life is recommended by Health Canada, the Dietitians of Canada, and the Canadian Pediatric Society
- breast milk is easily digested and has a low renal solute load
- immunologic
 - IgA, macrophages, active lymphocytes, lysozymes, lactoferrin (lactoferrin inhibits *E. coli* growth in intestine)
 - protection is greatest during early months, but is cumulative with increased duration of breastfeeding
 - lower allergenicity (decreased cow's milk protein allergy and eczema)
 - lower pH promotes growth of lactobacillus in the gastrointestinal tract (protective against pathogenic intestinal bacteria)
- parent-child bonding, economical, convenient

Complications of Breastfeeding

- mother
 - sore/cracked nipples: treat with warm compresses, massage, frequent feeds, soothing barrier creams (Desitin®, Vaseline®), proper latching technique
 - breast engorgement (usually in first week): continue breastfeeding and/or pumping
 - mastitis (usually due to *S. aureus*): treat with cold compresses between feeds, cloxacillin for mother, continue nursing, ± incision and drainage
- infant
 - breastfeeding jaundice (first 1-2 weeks): due to lack of milk production and subsequent dehydration (see *Jaundice*, P70)
 - breast milk jaundice: rare (0.5% of newborns, persists up to 4-6 months); not fully understood, thought to be due to substances in breast milk that inhibit conjugation of bilirubin or increased enterohepatic circulation of bilirubin
 - poor weight gain: consider dehydration or failure to thrive
 - oral candidiasis (thrush): check baby's mouth for white cheesy material that does not scrape off; treat baby with antifungal such as nystatin (Mycostatin®) (treat mother topically to prevent transmission)

Infant Growth and Health Outcomes Associated with 3 Months Compared with 6 Months of Exclusive Breastfeeding

The American Journal of Clinical Nutrition 2003; 78:291-295

Purpose: To compare differences in growth and health in infants exclusively breastfed for 3 versus 6 months.

Study: Observational cohort study with 3483 term newborns

Results: The rate of gastrointestinal infections was significantly reduced in the group of infants who were exclusively breastfed for 6 months. This finding was limited to the period between 3 and 6 months of age (adjusted IOR 0.35 (95% CI: 0.13, 0.96)). The breastfed babies were smaller at 6 months but there was no difference in growth between the two groups by 12 months. No significant association was found between breastfeeding and the rate of eczema or respiratory infections.

Conclusions: There is an association between breastfeeding and a lower incidence of gastrointestinal infections in term infants.

Alternatives to Breastfeeding

Table 4. Infant Nutrition Source

Type of Nutrition	Indication(s)	Content (compared to breast milk)
Breast milk	Most babies	70:30 whey:casein ratio Fat from dietary butterfat Carbohydrate from lactose
Cow's milk based (Enfamil®, Similac®)	Premature babies Transitional Contraindication to breastfeeding	Plant fats instead of dietary butterfat Lower whey:casein ratio
Fortified formula	Low birth weight Premature babies	More calories Higher amounts of vitamins A, C, D, K May only be used in hospital due to risk of fat-soluble vitamin toxicity
Soy protein (Isomil®, Prosobee®)	Galactosemia Lactose intolerance	Corn syrup solids or sucrose instead of lactose
Partially hydrolyzed proteins (Good Start®)	Delayed gastric emptying Risk of cow's milk allergy	Protein is 100% whey with no casein
Protein hydrolysate (Nutramigen®, Alimentum®, Pregestimil®, Portagen®)	Malabsorption Food allergy	Protein is 100% casein with no whey Corn syrup solids, sucrose, OR tapioca starch instead of lactose Expensive
Amino acid (Neocate®)	Food allergy Short gut	No proteins, just free amino acids Corn syrup solids instead of lactose Very expensive
Metabolic	Inborn errors of metabolism	Various different compositions for children with galactosemia, propionic acidemia, etc.

Most formulas contain 670 calories per litre. The healthy term infant requires ~100 cal/kg/d for 0-6 mos and ~80 cal/kg/d for 6-12 mos. "Fortified" formulas for premature babies may contain more calories. Formula may also be supplemented with specific nutrients in babies with malabsorption syndromes. True lactose intolerance is extremely rare in children under age 5.

Infant Feeding

Table 5. Dietary Schedule

Age	Food	Comments
0 to 4-6 months	Breast milk, formula	
4 to 9 months	Iron enriched cereals	Rice cereals first because less allergenic
	Pureed vegetables	Yellow/orange vegetables first and green last (more bulky) Avoid vegetables with high nitrite content (beets, spinach, turnips) Introduce vegetables before fruit (alternate yellow and green vegetables daily)
	Pureed fruits	Avoid juices
	Pureed meats, fish, poultry, egg yolk	
9 to 12 months	Finger foods, peeled fruit, cheese and cooked vegetables, homo milk	No honey until >12 months (risk of botulism)
		No peanuts or raw, hard vegetables until age 3 to 4 years
		No added sugar, salt, fat or seasonings

- do not delay introduction of solid foods beyond 9 months
- introduce 2-3 new foods per week (easier to identify adverse reactions) and allow a few days between each introduction
- avoid excessive milk/juice intake when >1 year



Restriction of allergenic foods (e.g. egg whites and nuts products) in the first year of life is controversial. There is a recent trend towards early introduction of these foods.



8 Major Choking Hazards up to the Age of 4:

1. Hot dogs (uncut)
2. Grapes (uncut)
3. Carrots/other raw vegetables
4. Nuts
5. Fish with bones
6. Popcorn
7. Hard candies
8. Gum



Scoliosis Screening

Despite mass school screening implemented in parts of the USA and Canada in the 1970s-90s, the Canadian (1994) and American (2004) Task Forces on Preventive Health Care do NOT currently recommend routine screening using the Forward Bend Test (FBT). Cohort studies indicate that the forward bend test has poor sensitivity for identifying pathological curves (Karachalios et al. 1999, Yawn et al. 1999, Pruijs et al. 1996). Furthermore, there is no evidence to suggest that screening and increased bracing lead to better outcomes.



Term newborn should gain 20-30 g/day.



To estimate weight of child > 1 year (kg)
~ Age x 2 + 8



Head Circumference

Remember 3, 9, and Multiples of 5:

Newborn 35 cm
3 mos 40 cm
9 mos 45 cm
3 yrs 50 cm
9 yrs 55 cm

Normal Physical Growth

- newborn size influenced by maternal factors (placenta, in utero environment)
- premature infants (<37 weeks): use corrected gestational age until 2 years
- not linear: most rapid growth during first two years and growth spurt at puberty
- different tissue growth at different times
 - first two years: CNS
 - mid-childhood: lymphoid tissue
 - puberty: gonadal maturation (testes, breast tissue)
- body proportions: upper/lower segment ratio – midpoint is symphysis pubis
 - newborn 1.7; adult male 0.97; adult female 1.0
- poor correlation between birth weight and adult weight

Table 6. Average Growth Parameters

	Normal	Growth	Comments
Birth Weight	3.25 kg (7 lbs)	2 x birth wt by 4-5 mos 3 x birth wt by 1 year 4 x birth wt by 2 years	Weight loss (up to 10% of birth wt) in first 7 days of life is normal Neonate should regain birth weight by ~10 days of age
Length/Height	50 cm (20 in)	25 cm in 1st year 12 cm in 2nd year 8 cm in 3rd year then 4-7 cm/year until puberty 1/2 adult height at 2 years	Measure supine length until 2 years of age, then measure standing height
Head Circumference	35 cm (14 in)	2 cm/month for 1st 3 mos 1 cm/month at 3-6 mos 0.5 cm/month at 6-12 mos	Measure around occipital, parietal, and frontal prominences to obtain the greatest circumference

Dentition

- primary dentition (20 teeth)
 - first tooth at 5-9 months (lower incisor), then 1 per month until 20 teeth
 - 6-8 central teeth by 1 year
- secondary dentition (32 teeth)
 - first adult tooth is 1st molar at 6 years, then lower incisors
 - 2nd molars at 12 years, 3rd molars at 18 years

Failure to Thrive (FTT)

Table 7. Failure to Thrive Patterns

Growth Parameters			Suggestive Abnormality	
Decreased Wt	Normal Ht	Normal HC	Caloric insufficiency Decreased intake	Hypermetabolic state Increased losses
Decreased Wt	Decreased Ht	Normal HC	Structural dystrophies Endocrine disorder	Constitutional growth delay Familial short stature
Decreased Wt	Decreased Ht	Decreased HC	Intrauterine insult	Genetic abnormality

HC = head circumference; Ht = height; Wt = weight

Definition

- weight <3rd percentile, or falls across two major percentile curves, or <80% of expected weight for height and age
- inadequate caloric intake most common factor in poor weight gain
- may have other nutritional deficiencies (e.g. protein, iron, vitamin D)
- **history**
 - duration of problem and growth history
 - detailed dietary and feeding history, appetite, behaviour before and after feeds, bowel habits
 - pregnancy, birth, and postpartum history; developmental and medical history (including medications); social and family history (parental height, weight, growth pattern)
 - assess 4 areas of functioning: child's temperament, child-parent interaction, feeding behaviour and parental psychosocial stressors
- **physical exam**
 - height (Ht), weight (Wt), head circumference (HC), arm span, upper-to-lower (U/L) segment ratio
 - assessment of nutritional status, dysmorphism, Tanner stage, evidence of chronic disease
 - observation of a feeding session and parent-child interaction
 - signs of abuse or neglect



Energy Requirements

- 0-10 kg: 100 cal/kg/day
- 1-20 kg: 1,000 cal + 50 cal/kg/day for each kg > 10
- +20 kg: 1,500 cal + 20 cal/kg/day for each kg > 20



Upper to Lower (U/L) Segment Ratio is...

Increased in achondroplasia, short limb syndromes, hypothyroid, storage diseases.

Decreased in Marfan, Klinefelter, Kallman, testosterone deficiency.



Calculating Upper to Lower (U/L) Segment Ratio

Upper segment: Top of head to pubic symphysis.

Lower segment: Pubic symphysis to floor.

U/L: upper segment/lower segment.

- **investigations (as indicated by clinical presentation)**
 - CBC, blood smear, electrolytes, urea, ESR, T4, TSH, urinalysis
 - bone age x-ray (left wrist – compared to standardized wrist x-rays)
 - karyotype in all short girls and in short boys where appropriate
 - any other tests indicated from history and physical exam: renal or liver function tests, venous blood gases, ferritin, immunoglobulins, sweat chloride, fecal fat

Organic FTT (10%)

- inability to feed
 - insufficient breast milk production
 - poor retention (GERD, vomiting)
 - CNS, neuromuscular, mechanical problems with swallowing and sucking
 - anorexia (associated with chronic disease)
- inadequate absorption (see *Pediatric Gastroenterology*, P39)
 - malabsorption: celiac disease, cystic fibrosis (CF), pancreatic insufficiency
 - loss from the GI tract: chronic diarrhea, vomiting
- inappropriate utilization of nutrients
 - renal loss: e.g. tubular disorders
 - inborn errors of metabolism
 - endocrine: type 1 diabetes, diabetes insipidus (DI), hypopituitarism, congenital hypothyroidism
- increased energy requirements
 - pulmonary disease: CF
 - cardiac disease
 - endocrine: hyperthyroidism, DI, hypopituitarism
 - malignancies
 - chronic infections
 - inflammatory: systemic lupus erythematosus (SLE)
- decreased growth potential
 - specific syndromes, chromosomal abnormalities, GH deficiency
 - intrauterine insults: fetal alcohol syndrome (FAS), TORCH infections
- treatment: cause-specific



Clinical Signs of FTT

SMALL KID

Subcutaneous fat loss
Muscle atrophy
Alopecia
Lethargy
Lagging behind normal
Kwashiorkor
Infection (recurrent)
Dermatitis

Non-Organic FTT (90%)

- often due to malnutrition, inadequate nutrition, poor feeding technique, errors in making formula
- these children may present as picky eaters, with poor emotional support at home or poor temperamental “fit” with caregiver
- may have delayed psychomotor, language, and personal/social development
- emotional deprivation, poor parent-child interaction, dysfunctional home
- child abuse and/or neglect
- parental psychosocial stress, personal history of suffering abuse or neglect
- treatment: most are managed as outpatients with multidisciplinary approach
 - primary care physician, dietitian, psychologist, social work, child protection services

Obesity



- a quarter of Canadian children ages 2-17 are overweight or obese, 8% are obese (2004)

Definition

- BMI >95th percentile for age and height
- caused by a chronically positive energy balance (intake exceeds expenditure)

Risk Factors

- genetic predisposition:
 - if 1 parent is obese – 40% chance of obese child
 - if both parents are obese – 80% chance of obese child
- genetic heritability accounts for 25-40% of juvenile obesity

Clinical Presentation

- history: diet, activity, family heights and weights, growth curves
- body mass index (BMI) tends not to be used by pediatricians prior to adolescence
- physical examination: may suggest secondary cause, e.g. Cushing syndrome
- organic causes are rare (<5%)
 - genetic: e.g. Prader-Willi, Carpenter, Turner syndromes
 - endocrine: e.g. Cushing syndrome, hypothyroidism

Geographic and Demographic Variation in the Prevalence of Overweight Canadian Children
Obesity Research 2003; 11(5):668-73

Purpose: To determine geographic and demographic variation in the prevalence of overweight Canadian children.

Study: Assessment of trends in BMI using data from the 1981 Canadian Fitness Survey and the 1996 National Longitudinal Survey of Children and Youth.

Main Outcomes: The prevalence of overweight and obese children age 7 to 13 years, secular trends from 1981 to 1996 by province, and provincial variation after adjusting for socioeconomic and demographic characteristics.

Results: In 1996, 33% of boys and 26% of girls were classified as overweight, and 10% of boys and 9% of girls were classified as obese. The odds ratio associated with the 1981 to 1996 change in the prevalence of overweight children was 3.24 (95% CI, 2.83-3.70) for Canada as a whole. There are clear regional differences, with those in Atlantic Canada more likely to be overweight and Prairie children less likely. These differences were not sufficiently accounted for by differences in socioeconomic circumstances.

Conclusions: The prevalence of childhood obesity is increasing in all areas of Canada, although more so in Atlantic Canada.

- complications
 - childhood obesity is an unreliable predictor of adult obesity
 - ♦ unless >180% of ideal body weight
 - ♦ however, 70% of obese adolescents become obese adults
 - association with: hypertension, dyslipidemia, slipped capital femoral epiphysis, type 2 diabetes, asthma, obstructive sleep apnea
 - boys: gynecomastia
 - girls: polycystic ovarian disease, early menarche, irregular menses
 - psychological: teasing, decreased self-esteem, unhealthy coping mechanisms, depression
- management
 - encouragement and reassurance; engagement of entire family
 - diet: qualitative changes; do not encourage weight loss but allow for linear growth to catch up with weight; special diets used by adults are not encouraged
 - evidence against very low calorie diets for preadolescents
 - behaviour modification: increase activity, change eating habits/meal patterns
 - education: multidisciplinary approach, dietitian, counselling
 - surgery and pharmacotherapy are not used in children

Infantile Colic

- rule of 3's: unexplained paroxysms of irritability and crying for >3 hours/day and >3 days/week for >3 weeks in an otherwise healthy, well-fed baby
- occurs in 10% of infants
- etiology: generally regarded as a lag in the development of normal peristaltic movement in gastrointestinal tract; other theories suggest a lack of self-soothing mechanisms
- other reasons why babies cry: wet, hunger or gas pains, too hot or cold, overstimulated, need to suck or be held
- timing: onset 10 days to 3 months of age; peak 6-8 weeks
- child cries, pulls up legs and passes gas soon after feeding
- management
 - parental relief, rest and reassurance
 - hold baby, soother, car ride, music, vacuum, check diaper
 - medications (Ovol® drops, gripe water) of no proven benefit
 - if breastfeeding, elimination of cow's milk protein from mother's diet (effective in very small percentage of cases)
 - try casein hydrolysates formula (Nutramigen®)

Milk Caries

- decay of superior front teeth and back molars in first 4 years of life
- often occur in children put to bed with a bottle of milk or juice
- can also be caused by breastfeeding (especially prolonged night feeds)
- prevention
 - no bottle at bedtime (unless plain water)
 - use water as thirst quenchers during the day, do not sweeten pacifier (>1 year)
 - can clean teeth with soft damp cloth or toothbrush and water
 - avoid fluoridated toothpaste until able to spit (>3 years) due to fluorosis risk (stains teeth)
 - Canadian Dental Association recommends assessment by dentist 6 months after eruption of first tooth, or by 1 year of age

Injury Prevention Counselling



- injuries are the leading cause of death in children >1 year of age
- main causes: motor vehicle crashes, burns, drowning, falls, choking, infanticide

Table 8. Injury Prevention Counselling

0-6 months	6-12 months	1-2 years	2-5 years
Do not leave alone on bed, on change table or in tub	Install stair barriers	Never leave unattended	Bicycle helmet
Keep crib rails up	Discourage use of walkers	Keep pot handles turned to back of stove	Never leave unsupervised at home, driveway or pool
Check water temp before bathing	Avoid play areas with sharp-edged tables and corners	No nuts, raw carrots, etc. due to choking hazard	Teach bike safety, stranger safety, and street safety
Do not hold hot liquid and infant at the same time	Cover electrical outlets	No running while eating	Swimming lessons, sunscreen, toddler seats in the car, fences around pools, dentist by age 3
Turn down hot water heater	Unplug appliances when not in use		
Check milk temp before feeding	Keep small objects, plastic bags, cleaning products, and medications out of reach		
Have appropriate car seats – required before allowed to leave hospital	Supervise during feeding		
• <9 kg: rear-facing			
• 10-18 kg: front-facing			
• 18-36.4 kg: booster seat			

- always have Poison Control number by telephone
- have smoke and carbon monoxide detectors in the house and check yearly

Poison Prevention

- keep all types of medicines, vitamins, and chemicals locked up in a secure container
- potentially dangerous: drugs, drain cleaners, furniture polish, insecticides, cosmetics, nail polish remover, automotive products
- do not store any chemicals in juice, soft drink, or water bottles
- keep alcoholic beverages out of reach: 3 oz hard liquor can kill a 2-year-old
- always read label before administering medicine to ensure correct drug and dose

Sudden Infant Death Syndrome (SIDS)



Definition

- sudden and unexpected death of an infant <12 months of age in which the cause of death cannot be found by history, examination or a thorough postmortem and death scene investigation

Epidemiology

- 0.5/1,000 (leading cause of death between 1-12 months of age); M:F = 3:2
- more common in children placed in prone position
- in full term infants, peak incidence is 2-4 months, 95% of cases occur by 6 months
- increase in deaths during peak respiratory syncytial virus (RSV) season
- most deaths occur between midnight and 8 AM

Risk Factors

- more common in prematurity, if smoking in household, minorities (higher incidence in aboriginals and African Americans), socially disadvantaged
- risk of SIDS is increased 3-5 times in siblings of infants who have died of SIDS

Prevention – “Back to Sleep, Front to Play”

- place infant on back, NOT in prone position when sleeping
- allow supervised play time daily in prone position
- alarms/other monitors not recommended – increase anxiety and do not prevent life-threatening events
- avoid overheating and overdressing
- appropriate infant bedding (firm mattress, avoid loose bedding and crib bumper pads)
- no smoking
- pacifiers appear to have a protective effect; do not reinsert if falls out



Apparent Life-Threatening Events (ALTEs)

A group of conditions often marked by an episode of apnea, cyanosis, change in tone, or change in mental status occurring in a child, where an observer fears the child may be dying. It is unclear whether or not there is a connection between ALTEs and SIDS, and a thorough workup should be done looking for a cause of the ALTE (e.g. infection, cardiac, neurologic)

Circumcision

- elective procedure to be performed only in healthy, stable infants
- contraindicated when genital abnormalities present (e.g. hypospadias) or known bleeding disorder
- usually performed for social or religious reasons (in Ontario, not covered by OHIP)
- complications (<1%): local infection, bleeding, urethral injury
- medical benefits include prevention of phimosis, slightly reduced incidence of UTI, balanitis, cancer of the penis
- 2 recent RCTs (*Lancet* 369, Feb 2007) suggested that routine circumcision significantly reduced HIV transmission (studies conducted in high endemic areas, i.e. Africa); circumcision also appears to reduce HPV transmission
- routine circumcision is not currently recommended by the CPS or AAP

Toilet Training

- 90% of kids attain bowel control before bladder control
- generally females train earlier than males
- 25% by 2 years old (in North America), 98% by 3 years old have daytime bladder control
- signs of toilet readiness:
 - ambulating independently, stable on potty, desire to be independent or to please caregivers (i.e. motivation), sufficient expressive and receptive language skills (2-step command level), can stay dry for several hours (large enough bladder)

Abnormal Child Behaviours



Elimination Disorders

ENURESIS

- involuntary urinary incontinence by day and/or night (typically by 5-6 years old)
- wetting at least twice a week for at least 3 consecutive months or causing significant distress to the child
- treatment should not be considered until 6 years of age; high rate of spontaneous cure
- should be evaluated if >6 years old; dysuria; change in gross colour, odour, stream; secondary or diurnal

Primary Nocturnal Enuresis

- wet only at night during sleep, can be normal up to age 6
- prevalence: 10% of 6-year olds, 3% of 12-year olds, 1% of 18-year olds
- developmental disorder or maturational lag in bladder control while asleep
- more common in boys, family history common
- treatment:
 - time and reassurance (~20% resolve spontaneously each year), behaviour modification (limiting nighttime fluids, voiding prior to sleep), engage child with rewards, bladder retention exercises, scheduled toileting
 - conditioning: "wet" alarm wakes child upon voiding (70% success rate)
 - medications (considered second line therapy): DDAVP by nasal spray or oral tablets (high relapse rate, costly), oxybutynin (Ditropan®), imipramine (Tofranil®) (rarely used, lethal if overdose, cholinergic side effects)

Secondary Enuresis

- develops after child has sustained period of bladder control (6 months or more)
- nonspecific regression in the face of stress or anxiety (e.g. birth of sibling, significant loss, family discord)
- may also be secondary to urinary tract infection (UTI), diabetes mellitus (DM), diabetes insipidus (DI), neurogenic bladder, cerebral palsy (CP), sickle cell disease, seizures, pinworms
- may occur if engrossed in other activities
- treatment depends on cause

Diurnal Enuresis

- daytime wetting (60-80% also wet at night)
- timid, shy, temperament problems
- most common cause: micturition deferral (holding urine until last minute)
- may also result from psychosocial stressors, rule out structural anomalies (e.g. ectopic ureteral site, neurogenic bladder), UTI, constipation, CNS disorders
- treatment: depends on cause; behavioural (scheduled toileting, double voiding, good bowel program), pharmacotherapy

ENCOPRESIS

- fecal incontinence in a child >4 years old, at least once per month for 3 months
- prevalence: 1-1.5% of school-aged children (rare in adolescence); M:F = 6:1 in school-aged children
- usually associated with chronic constipation
- must exclude medical causes (e.g. Hirschsprung disease, hypothyroidism, hypercalcemia, spinal cord lesions, anorectal malformations)

Retentive Encopresis

- causes
 - physical: anal fissure (painful stooling)
 - emotional: disturbed parent-child relationship, coercive toilet training, social stressors
- history
 - child withholds bowel movement, develops constipation, leading to fecal impaction and seepage of soft or liquid stool (overflow incontinence)
 - crosses legs or stands on toes to resist urge to defecate
 - distressed by symptoms, soiling of clothes
 - toilet training coercive or lacking in motivation
 - may show oppositional behaviour
- physical exam
 - digital rectal exam: large fecal mass in rectal vault
 - anal fissures (result from passage of hard stools)
- treatment
 - complete clean-out of bowel
 - ♦ enemas and suppositories
 - maintenance of regular bowel movements – compliance is crucial
 - ♦ stool softeners (e.g. Colace®, Lactulose®, Lansoyl®, mineral oil regularly)
 - ♦ diet modification (see *Pediatric Gastroenterology*, P40)
 - ♦ toilet schedule and positive reinforcement
 - assessment and guidance regarding psychosocial stressors
 - behavioural modification
- complications: continuing cycle, toxic megacolon (requires >3-12 months to treat), bowel perforation

Sleep Disturbances

Types of Sleep Disturbances

- insufficient sleep quantity
 - difficulty falling asleep (e.g. Limit Setting Sleep Disorder)
 - ♦ preschool and older children
 - ♦ bedtime resistance
 - ♦ due to caregiver's inability to set consistent bedtime rules and routines
 - ♦ often exacerbated by child's oppositional behaviours
- poor sleep quality
 - frequent arousals (e.g. Sleep Onset Association Disorder)
 - ♦ infants and toddlers
 - ♦ child learns to fall asleep only under certain conditions or associations (with parent, with light on, in front of television)
 - ♦ child loses ability to self soothe
 - ♦ during the normal brief arousal periods of sleep (q90-120 min), child cannot fall back asleep because same conditions are not present
- parasomnias
 - episodic nocturnal behaviours
 - often involves cognitive disorientation and autonomic/skeletal muscle disturbance
 - e.g. sleep walking, sleep terrors, nightmares

Management of Sleep Disturbances

- set strict bedtimes and "wind-down" routines
- do not send child to bed hungry
- always sleep in bed, in a dark, quiet and comfortable room, without "associations"
- do not use bedroom for timeouts
- systematic ignoring and gradual extinction for sleep onset association disorder
- positive reinforcement for limit setting sleep disorder

Nightmares

- prevalence: common in boys, 4-7 years old
- associated with REM sleep (anytime during night)
- upon awakening, child is alert and clearly recalls frightening dream
- may be associated with daytime stress/anxiety
- treatment: reassurance



Daily Sleep Requirement

• <6 months	16 hours
• 6 months	14.5 hours
• 12 months	13.5 hours
• 2 years	13 hours
• 4 years	11.5 hours
• 6 years	9.5 hours
• 12 years	8.5 hours
• 18 years	8 hours

Nap Patterns

- 2/day at 1 year
- 1/day at 2 years: 2-3 hours
- 0.5/day at 5 years: 1.7 hours

Night Terrors

- prevalence: 15% of children have occasional episodes
- abrupt sitting up, eyes open, screaming
- panic and signs of autonomic arousal
- occurs in early hours of sleep, non-REM, stage 4 of sleep
- no memory of event, parents unable to calm child
- stress/anxiety can aggravate them
- course: remits spontaneously at puberty
- treatment: reassurance for parents

Breath-Holding Spells

- occur in 0.1-5% of healthy children 6 months-4 years of age
- spells usually start during first year of life
- 2 types
 - cyanotic (more common), usually associated with anger/frustration
 - pallid, usually associated with pain/surprise
- child is provoked (usually by anger, injury or fear), starts to cry and then becomes silent
- spell resolves spontaneously or the child may lose consciousness; rarely progresses to seizures
- treatment: behavioural – help child control response to frustration and avoid drawing attention to spell; avoid being too permissive in fear of precipitating a spell

Approach to the Crying/Fussing Child

History

- description of infant's baseline feeding, sleeping, crying patterns
- infectious symptoms – fever, tachypnea, rhinorrhea, ill contacts
- feeding intolerance – gastroesophageal reflux with esophagitis
- nausea, vomiting, diarrhea, constipation
- trauma
- recent immunizations (vaccine reaction) or medications (drug reactions), including maternal drugs taken during pregnancy (neonatal withdrawal syndrome), and drugs that may be transferred via breast milk
- inconsistent history, pattern of numerous emergency department (ED) visits, high-risk social situations all raise concern of abuse

Physical Examination

- perform a thorough head-to-toe exam with the child completely undressed

Table 9. The Physical Examination of the Crying/Fussing Child

Organ System	Examination Findings	Possible Diagnosis
HEENT	Bulging fontanelle	Meningitis, shaken baby syndrome
	Blepharospasm, tearing	Corneal abrasion
	Retinal hemorrhage	Shaken baby syndrome
	Oropharyngeal infections	Thrush, gingivostomatitis, herpangina, otitis media
Neurologic	Irritability or lethargy	Meningitis, shaken baby syndrome
Cardiovascular	Poor perfusion	Sepsis, anomalous coronary artery, meningitis, myocarditis, congestive heart failure (CHF)
	Tachycardia	Supraventricular tachycardia
Respiratory	Tachypnea	Pneumonia, CHF
	Grunting	Respiratory disease, response to pain
Abdominal	Mass, empty RLQ	Intussusception
Genitourinary	Scrotal swelling	Incarcerated hernia, testicular torsion
	Penile/clitoral swelling	Hair tourniquet
Rectal	Anal fissure	Constipation or diarrhea
	Hemoccult positive stool	Intussusception, necrotizing enterocolitis, volvulus
Musculoskeletal	Point tenderness or decreased movement	Fracture, syphilis, osteomyelitis, toe/finger hair tourniquet

Dermatology

Table 10. Common Paediatric Rashes

Type of Rash	Differential	Appearance
Diaper Dermatitis	Irritant contact dermatitis	Shiny, red macules/patches, no flexural involvement
	Seborrheic dermatitis	Yellow, greasy macules/plaques on erythema, scales
	Candidal dermatitis	Erythematous macerated papules/plaques, satellite lesions
Other Dermatitis	Atopic dermatitis	Erythematous papules/plaques, oozing, excoriation, lichenification, classic areas of involvement
	Nummular dermatitis	Annular erythematous plaques, oozing, crusting
	Allergic contact dermatitis	Red papules/plaques/vesicles/bullae, only in area of allergen
	Irritant contact dermatitis	Morphology depends on irritant
	Dyshidrotic dermatitis	Papulovesicular, cracking/fissuring, hands and feet ("Tapioca pudding")
	Seborrheic dermatitis	See above, sebaceous areas such as nasolabial folds and scalp
Papulosquamous Eruptions	Psoriasis	Erythematous plaques with silvery scales, nail pitting/onycholysis
	Pityriasis rosea	Salmon-pink plaques, herald patch with smaller papules ("Christmas tree" pattern)
Infectious	Scabies	Polymorphic (red excoriated papules/nodules, burrows), in web spaces/folds, very pruritic
	Impetigo	Honey-coloured crusts or superficial bullae
	Tinea corporis	Round erythematous plaques, central clearing and scaly border
Exanthems (see Dermatology, D40)		
Drug Reactions (see Dermatology, D22)		
Acne (see Dermatology, D12)		

Child Abuse and Neglect



Definition

- an act of commission (abuse – physical, sexual, or psychological) or omission (neglect) by a caregiver that harms a child

Legal Duty to Report

- upon reasonable grounds to suspect abuse and/or neglect, physicians are required by law to contact the Children's Aid Society (CAS) personally to disclose all information
- duty to report overrides patient confidentiality; physician is protected against liability
- ongoing duty to report: if there are additional reasonable grounds to suspect abuse and/or neglect, a further report to the CAS must be made

Risk Factors

- environmental factors
 - social isolation
 - poverty
 - domestic violence
- caregiver factors
 - parents were abused as children
 - psychiatric illness
 - substance abuse
 - single parent family
 - poor social and vocational skills, below average intelligence
- child factors
 - difficult temperament
 - disability, special needs (e.g. developmental delay)
 - premature



"If no cruising, no bruising."



Presentation of Neglect

- Failure to thrive, developmental delay
- Inadequate or dirty clothing, poor hygiene
- Child exhibits poor attachment to parents, no stranger anxiety

Presentation of Physical Abuse

- history inconsistent with physical findings, or history not reproducible
- delay in seeking medical attention
- injuries of varied ages, recurrent or multiple injuries
- distinctive marks: belt buckle, cigarette burns, hand prints
- patterns of injury: bruises on the face, abdomen, buttocks, genitalia, upper back; posterior rib fractures; immersion burns (e.g. hot water)
- altered mental status: head injury, poisoning
- physical findings not consistent with any underlying medical condition
- shaken baby syndrome
 - violent shaking of infant resulting in intracranial hemorrhages, retinal hemorrhages, and posterior rib fractures
- head trauma is the leading cause of death in child maltreatment

Sexual Abuse

- prevalence: 1 in 4 females, 1 in 10 males
- peak ages at 2-6 and 12-16 years
- most perpetrators are male and known to child
 - in decreasing order: family member, non-relative known to victim, stranger
- presentation
 - disclosure: diagnosis usually depends on child telling someone
 - psychosocial: specific or generalized fears, depression, nightmares, social withdrawal, lack of trust, low self-esteem, school failure, sexually aggressive behaviour, advanced sexual knowledge, sexual preoccupation or play
 - physical signs: recurrent UTIs, pregnancy, STIs, vaginitis, vaginal bleeding, pain, genital injury, enuresis
- investigations depend on presentation, age, sex, and maturity of child
 - sexual assault examination kit within 24 hours if prepubertal, within 72 hours if pubertal
 - rule out STI, UTI, pregnancy (consider STI prophylaxis or morning after pill)
 - rule out other injuries (vaginal/anal/oral penetration, fractures, head trauma)

Management of Child Abuse and Neglect

- history
 - from child and each caregiver separately (if possible)
- physical exam
 - head to toe (do not force)
 - emotional state
 - development
 - document and/or photograph all injuries: type, location, size, shape, colour, pattern
 - be aware of "red herrings" (e.g. Mongolian blue spots vs. bruises)
- investigations
 - blood tests to rule out medical causes (e.g. thrombocytopenia or coagulopathy)
 - STI work-up
 - skeletal survey/bone scan
 - CT/MRI
 - fundoscopy to rule out retinal hemorrhage
- report all suspicions to CAS; request emergency visit if imminent risk to child or any siblings in the home
- acute medical care: hospitalize if indicated or if concerns about further or ongoing abuse
- arrange consultation to social work and appropriate follow-up
- may need to discharge child directly to CAS or to responsible guardian under CAS supervision

Adolescent Medicine



Normal Sexual Development

- puberty occurs with the maturation of the hypothalamic–pituitary–gonadal axis
- increases in the pulsatile release of gonadotropin hormone (GnRH) → increased release of LH and FSH → maturation of gonads and release of sex steroids → secondary sexual characteristics
- also requires adrenal production of androgens

Females

- occurs between age 8-13 years (may start early as 6 years in African-American girls)
- usual sequence
 - thelarche: breast budding (breast asymmetry may occur as one breast may grow faster than the other; becomes less noticeable as maturation continues)
 - adrenarche: axillary hair, body odour, mild acne
 - growth spurt
 - menarche: mean age 13 years; occurs 2 years after breast development and indicates that growth spurt is almost complete (Tanner Stage 4)
- early puberty is common and often constitutional, late puberty is rare

Males

- occurs between age 9-14 years (starts 1 years later than in girls)
- usual sequence
 - testicular enlargement
 - penile enlargement: occurs at Tanner Stage 4
 - adrenarche: axillary and facial hair, body odour, mild acne
 - growth spurt: occurs later in boys (Tanner Stage 4)
- early puberty is uncommon (need to rule out organic disease) but late puberty is common and often constitutional



Adolescent Psychosocial Assessment

HEEADSSS

Home
Education/Employment
Eating
Activities
Drugs
Sexuality
Suicide and depression
Safety

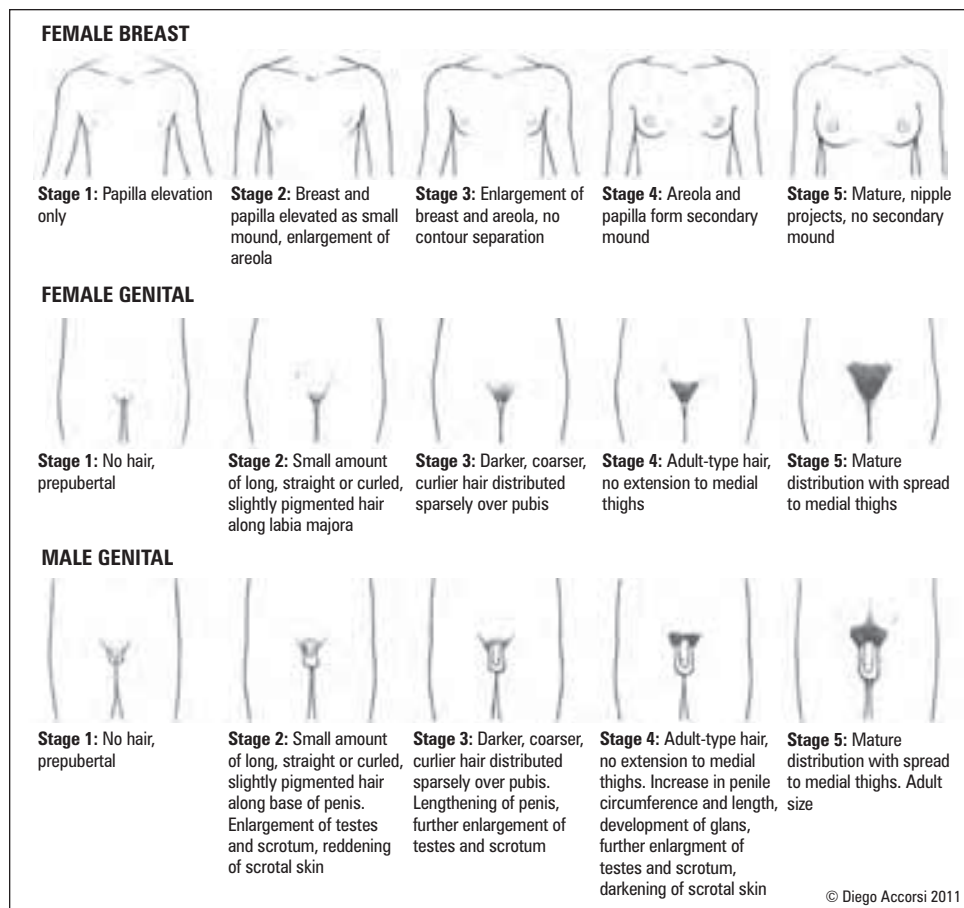


Figure 1. Tanner Staging

Normal Variation in Puberty

Premature Thelarche

- isolated breast tissue development in girls 6 months to 2 years
- requires careful history and physical to ensure no other estrogen effects or other signs of puberty (e.g. growth spurt)
- may be due to increased sensitivity to estrogen
- requires observation and periodic examinations every 6-12 months to ensure no further signs of puberty

Physiologic Leukorrhea

- occurs in the 6 months prior to menarche; scant mucoid, clear to milky vaginal discharge, not associated with pruritis or foul odour
- due to stimulation of endometrial glands by estrogen

Irregular Menstruation

- menses may be irregular in duration and length of cycle
- on average it takes 18 months to go through the first 12 periods
- birth control pills should be avoided as treatment

Premature Adrenarche

- usually develops in boys and girls before the age of 6, benign self-limiting condition
- adrenal production of DHEAS (precursor of androstenedione, testosterone and estrogen) reaches pubertal levels at an earlier age
- pubic and axillary hair, body odour, mild acne
- determine whether other signs of puberty are present (girls – thelarche; boys – testicular enlargement)
- exclude androgen secreting tumours (investigations: DHEAS levels, androstenedione, testosterone, bone age)

Gynecomastia

- transient development of breast tissue in boys
- common self-limited condition seen in 50% of male adolescents during puberty
- must distinguish true breast tissue from fat: 1-3 cm round, mobile, sometimes tender, firm mass under areola
- discharge from nipple or fixed mass should be investigated

Other Adolescent Medicine Topics

- Substance Abuse – see [Psychiatry](#), PS20
- Eating Disorders – see [Psychiatry](#), PS29
- Depression/Suicide – see [Psychiatry](#), PS7, PS34
- Sexually Transmitted Infections – see [Gynecology](#), GY26

Cardiology



Heart Murmurs

- 50-80% of children have audible heart murmurs at some point in their childhood
- most childhood murmurs are functional (e.g. “innocent”) without associated structural abnormalities and have normal ECG and radiologic findings
- in general, murmurs can become audible or accentuated in high output states, e.g. fever, anemia

Table 11. Differentiating Innocent and Pathological Heart Murmurs

	Innocent	Pathological
History and Physical	Asymptomatic	Symptoms and signs of cardiac disease (FTT, exercise intolerance)
Timing	Systolic ejection murmur (SEM)	All diastolic, pansystolic, or continuous (except venous hum)
Grade	<3/6	≥3/6 (palpable thrill)
Splitting	Physiologic S2	May have fixed split or single S2
Extra sounds/Clicks	None	May be present
Change of Position	Murmur varies	Unchanged

Table 12. Five Innocent Heart Murmurs

Type	Description	Age	Differential Diagnosis
Peripheral Pulmonic Stenosis	Neonates, low-pitched, radiates to axilla and back	Neonates, usually disappears by 3-6 mos	Patent Ductus Arteriosus (PDA) Pulmonary stenosis
Still's Murmur	Vibratory, lower left sternal border (LLSB) or apex, SEM	3-6 yrs	Subaortic stenosis Small ventricular septal defect (VSD)
Venous Hum	Infraclavicular hum, continuous, R>L	3-6 yrs	PDA
Pulmonary Ejection	Soft, blowing, left upper sternal border (LUSB), SEM	8-14 yrs	Atrial septal defect (ASD) Pulmonary stenosis
Supraclavicular Arterial Bruit	Low intensity, above clavicles	Any age	Aortic stenosis Bicuspid aortic valve

Congenital Heart Disease (CHD)

PRENATAL CIRCULATION

Before Birth

- fetal lungs bypassed by flow through fetal shunts:
 - shunting deoxygenated blood
 - ductus arteriosus: connection between pulmonary artery and aorta
 - shunting oxygenated blood
 - foramen ovale: connection between R and L atria
 - ductus venosus: connecting between umbilical vein and IVC
- circulation:
 - placenta (oxygenated blood) → umbilical vein → ductus venosus → IVC → R atrium → oxygenated blood shunted through foramen ovale → L atrium → L ventricle → aorta → brain/myocardium/upper extremities
 - deoxygenated blood returns via SVC to R atrium → 1/3 of blood entering R atrium does not flow through foramen ovale and flows to the R ventricle → pulmonary arteries → ductus arteriosus → aorta → systemic circulation → placenta for reoxygenation



Fetal circulation is designed so that oxygenated blood is preferentially delivered to the brain and myocardium.

At Birth

- with first breath, lungs open up and pulmonary resistance decreases allowing pulmonic blood flow
- with separation of low resistance placenta, systemic circulation becomes a high resistance system and the ductus venosus closes
- with closure of the fetal shunts and changes in pulmonic/systemic resistance, infant circulation assumes normal adult flow
- increasing pulmonic flow increases left atrial pressures leading to foramen ovale closure
- increased oxygen concentration in blood after first breath leads to decreased prostaglandins leading to closure of the ductus arteriosus

Embryologic Development

- most critical period of fetal heart development is between 3-8 weeks gestation
- single heart tube grows rapidly forcing it to bend back upon itself and begin to assume the shape of a four chambered heart
- insults at this time are most likely to lead to CHD

Epidemiology

- 8/1,000 live births can present with heart murmur, heart failure, or cyanosis
- ventricular septal defect is the most common lesion

Table 13. Risk Factors for Common CHD

Infant factors/Genetic conditions		Maternal Factors	
Abnormality	Dominant cardiac defect	Abnormality (% risk)	Dominant cardiac defect
Prematurity	PDA	Prior child with CHD (2-4% risk)	
CHARGE association	TOF, AVSD, ASD, VSD	TORCH esp. rubella (35%)	PDA, PS
DiGeorge	Aortic arch anomaly	Diabetes Mellitus (2-3%)	TGA, coarctation, VSD
Down syndrome	AVSD, VSD, ASD, TOF	PKU (25-50%)	TOF
Ehlers-Danlos	Mitral prolapse, dilated aortic root	SLE (20-40%)	Complete heart block
Kartagener's	Dextrocardia	Alcohol (25-30%)	ASD, VSD
Marfan	Mitral prolapse, aortic dissection or insufficiency, dilated aortic root		
Noonan	PS, ASD	Medications: Phenytoin	VSD, ASD, PS, AS, coarctation
Osteogenesis Imperfecta	Aortic incompetence	Medications: Valproate	Coarctation, HLHS, AS, VSD
Turner	Coarctation, bicuspid aortic valve	Medications: Retinoic acid	Aortic arch abnormalities

VSD = ventricular septal defect; ASD = atrial septal defect; PDA = patent ductus arteriosus; TOF = tetralogy of Fallot; TGA = transposition of great arteries; PS = pulmonary stenosis; AS = aortic stenosis; HLHS = hypoplastic left heart syndrome; AVSD = atrioventricular septal defect

Investigations

- echo, ECG, CXR

Characteristic Chest X-Ray Findings in Congenital Heart Disease

- Boot-Shaped Heart – Tetralogy of Fallot, Tricuspid Atresia
- Egg-Shaped Heart – Transposition of Great Arteries
- "Snowman" Heart – Total Anomalous Pulmonary Venous Return

CYANOTIC VS. ACYANOTIC CONGENITAL HEART DISEASE

- cyanosis: blue mucous membranes, nail beds, and skin secondary to an absolute concentration of deoxygenated hemoglobin of at least 3 g/dL
- **cyanotic heart disease:** (i.e. R to L shunt) blood bypasses the lungs → no oxygenation occurs → high levels of deoxygenated hemoglobin enters the systemic circulation → cyanosis
- **acyanotic heart disease:** (i.e. L to R shunt, obstruction occurring beyond lungs) blood passes through pulmonic circulation → oxygenation takes place → low levels of deoxygenated blood in systemic circulation → no cyanosis

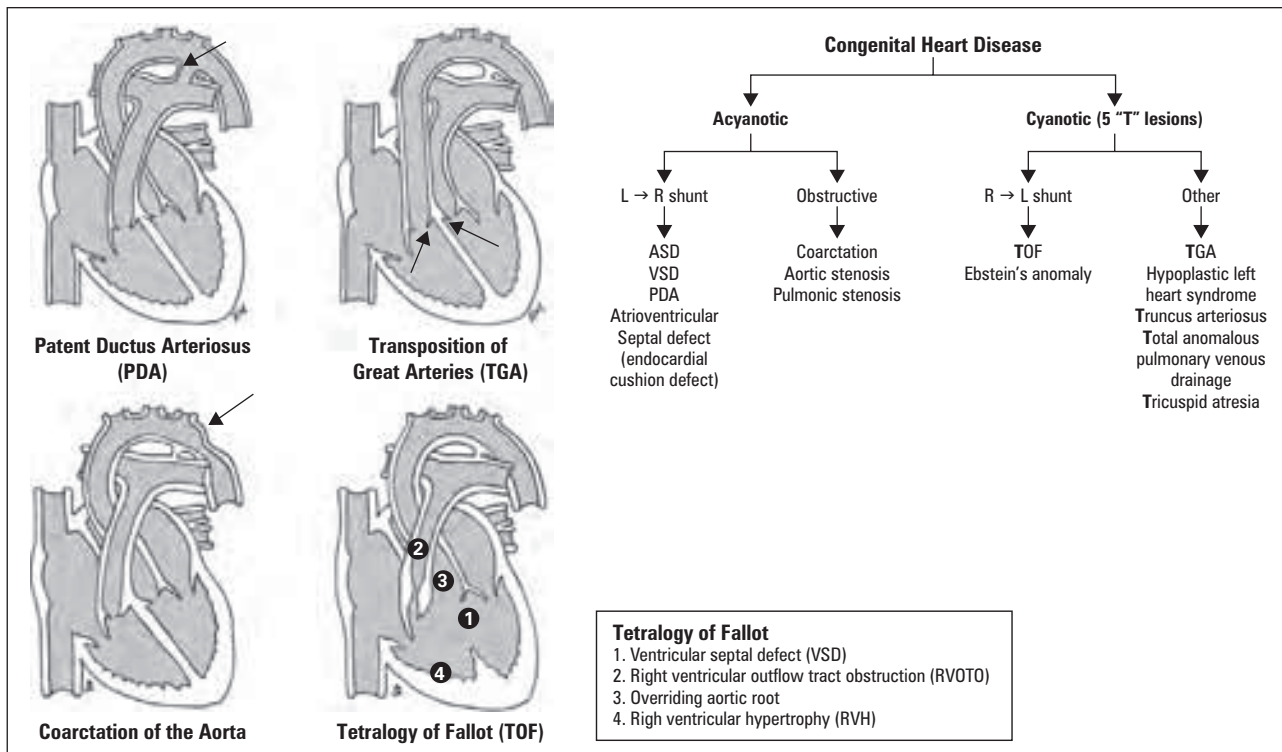


Figure 2. Common Congenital Heart Diseases

Acyanotic Congenital Heart Disease

1. LEFT TO RIGHT SHUNT LESIONS

- extra blood is displaced through a communication from the left to the right side of the heart → increased pulmonary blood flow → increased pulmonary pressures
- shunt volume dependent upon three factors: size of defect, pressure gradient between chambers or vessels, peripheral outflow resistance
- untreated shunts can result in pulmonary vascular disease, left ventricular dilatation and dysfunction, right ventricular hypertension and hypertrophy (RVH), and eventually R to L shunts

Atrial Septal Defect (ASD)

- three types: ostium primum (common in Down syndrome), ostium secundum (most common type, 50-70%), sinus venosus (defect located at entry of superior vena cava into right atrium)
- epidemiology: 6-8% of congenital heart lesions
- natural history: 80-100% spontaneous closure rate if ASD diameter <8 mm
- if remains patent, congestive heart failure (CHF) and pulmonary hypertension can develop in adult life
- history: often asymptomatic in childhood
- physical exam: grade 2-3/6 pulmonic outflow murmur (SEM), a mid-diastolic rumble at the left lower sternal border, and a widely split and fixed S2
- investigations
 - ECG: right axis deviation (RAD), mild RVH, right bundle branch block (RBBB)
 - CXR: increased pulmonary vasculature
- treatment: elective surgical or catheter closure between 2-5 years of age

Ventricular Septal Defect (VSD)

- most common congenital heart defect (30-50% of CHD)

Small VSD (majority)

- history: asymptomatic, normal growth and development
- physical exam: early systolic to holosystolic murmur, best heard at left lower sternal border (LLSB)
- investigations: ECG and CXR are normal
- treatment: most close spontaneously

Moderate-to-large VSD

- natural history: secondary pulmonary hypertension, CHF by 2 months of age
- history: delayed growth and development, decreased exercise tolerance, recurrent URIs or "asthma" episodes, CHF
- physical exam: holosystolic murmur at LLSB with thrill, mid-diastolic rumble at apex, size of VSD is inversely related to intensity of murmur
- investigations:
 - ECG: left ventricular hypertrophy (LVH), left atrial hypertrophy (LAH), RVH
 - CXR: increased pulmonary vasculature, cardiomegaly, CHF
- treatment: treatment of CHF and surgical closure by 1 year of age



Moderate-to-large VSD

Size of VSD is inversely related to intensity of murmur.

Patent Ductus Arteriosus (PDA)

- patent vessel between descending aorta and left pulmonary artery
- epidemiology
 - functional closure within first 15 hours of life, anatomical closure within first days of life
 - 5-10% of all congenital heart defects
 - delayed closure of ductus is common in premature infants (1/3 of infants <1750 grams); this is different from PDA in term infants
 - natural history: spontaneous closure common in premature infants, less common in term infants
- history: may be asymptomatic, or have apneic or bradycardic spells, poor feeding, accessory muscle use
- physical exam: tachycardia, bounding pulses, hyperactive precordium, wide pulse pressure, continuous "machinery" murmur best heard at left infraclavicular area
- investigations
 - ECG: may show LAE, LVH, RVH
 - CXR: normal to mildly enlarged heart, increased pulmonary vasculature, prominent pulmonary artery
 - diagnosis by echocardiography
- treatment
 - indomethacin (Indocin®) – PGE2 antagonist (PGE2 maintains ductus arteriosus patency) only effective in premature infants if necessary
 - catheter or surgical closure if PDA is contributing to respiratory compromise, poor growth or persists beyond 3rd month of life



Physical Exam for PDA (in term infant)

Heavy "machinery" murmur
High pulse rate
Wide pulse pressure
Hyperactive precordium
Big bounding pulse

Endocardial Cushion Defect (Atrioventricular [AV] Canal)

- spectrum from endocardial cushion VSD and ostium primum ASD to complete AV canal with common AV valve
- commonly associated with Down syndrome
- treatment
 - natural history depends on size of defect and valvular involvement, and should be repaired by age 6 months to prevent development of pulmonary hypertension
 - complete AV canal requires early complete surgical repair, preferably before 3 months of age

2. OBSTRUCTIVE LESIONS

- present with pallor, decreased urine output, cool extremities and poor pulses, shock or sudden collapse

Coarctation of the Aorta

- narrowing of aorta almost always at the level of the ductus arteriosus
- commonly associated with bicuspid aortic valve (50%); Turner syndrome (35%)
- few have high BP in infancy (160-200 mmHg systolic) but this decreases as collaterals develop
- if severe, presents with shock in the neonatal period when the ductus closes
- history: often asymptomatic
- physical exam: upper extremity systolic pressures of 140-145 mmHg, decreased blood pressure and weak/absent pulses in lower extremities, radial-femoral delay, absent or systolic murmur with late peak at apex, left axilla, and left back
- investigations: ECG – RVH early in infancy, LVH later in childhood
- prognosis and treatment
 - if associated with other lesions (e.g. PDA, VSD) can cause CHF
 - complications: hypertension
 - management: give prostaglandins to keep ductus arteriosus patent for stabilization, balloon arterioplasty or surgical correction in symptomatic neonate

Aortic Stenosis

- valvular (75%), subvalvular (20%), supravalvular and idiopathic hypertrophic subaortic stenosis (IHSS) (5%)
- history: often asymptomatic but may be associated with CHF, exertional chest pain, syncope or sudden death
- physical exam: SEM at right upper sternal border (RUSB) with aortic ejection click at the apex
- treatment
 - surgical repair if infant with critical aortic stenosis or older child with symptoms or peak gradient >50 mmHg
 - exercise restriction required

Pulmonary Stenosis

- valvular (90%), subvalvular, or supravalvular
- usually part of other congenital heart lesions (e.g. Tetralogy of Fallot) or in association with other syndromes (e.g. congenital rubella, Noonan syndrome)
- critical pulmonic stenosis: inadequate pulmonary blood flow, dependent on ductus for oxygenation, progressive hypoxia and cyanosis
- history: spectrum from asymptomatic to CHF
- physical exam: wide split S2 on expiration, SEM at LUSB, pulmonary ejection click
- investigations
 - ECG: RVH
 - CXR: dilated post-stenotic pulmonary artery
- treatment: surgical repair if critically ill or severe PS, or if presence of symptoms in older infants/children

Cyanotic Congenital Heart Disease

- systemic venous return re-enters systemic circulation directly
- most prominent feature is cyanosis (O_2 sat <75%)
- differentiate between cardiac and other causes of cyanosis with hyperoxic test
 - obtain preductal, right radial ABG in room air, and repeat ABG after the child inspires 100% oxygen
 - if PaO_2 improves to greater than 150 mmHg, cyanosis less likely cardiac in origin
- survival depends on mixing via shunts (e.g. ASD, VSD, PDA)
- should not use O_2 for these lesions

1. RIGHT TO LEFT SHUNT LESIONS

Tetralogy of Fallot

- 10% of all CHD, most common cyanotic heart defect diagnosed beyond infancy
- embryologically, a single defect with hypoplasia of the conus causing:
 - VSD
 - right ventricle (RV) outflow tract obstruction (RVOTO) (e.g. pulmonary stenosis)
 - overriding aorta
 - RVH
- degree of RVOTO directly determines the direction and degree of shunt and therefore the extent of clinical cyanosis and degree of RVH
- infants may initially have a L → R shunt and therefore are not cyanotic but the RVOTO is progressive, resulting in increasing R → L shunting with hypoxemia and cyanosis
- history: hypoxic “tet” spells
 - primary pathophysiology is hypoxia, leading to increased pulmonary vascular resistance (PVR) and decreased systemic resistance, occurring in exertional states (e.g. crying, exercise)
 - paroxysm of rapid and deep breathing, irritability and crying
 - hyperpnea, increasing cyanosis often leading to deep sleep and decreased intensity of murmur (decreased flow across RVOTO)
 - peak incidence at 2-4 months of age
- if severe may lead to seizures, loss of consciousness, death (rare)
- management: O₂, knee-chest position, fluid bolus, morphine sulfate, propranolol
- physical exam: single loud S2 due to severe pulmonary stenosis (i.e. RVOTO)
- investigations
 - ECG: RAD, RVH
 - CXR: boot shaped heart (small PA, RVH), decreased pulmonary vasculature, right aortic arch (in 20%)
- treatment: surgical repair within first two years of life, or earlier if marked cyanosis, “tet” spells, or severe RV outflow tract obstruction



Tetralogy of Fallot

1. Ventricular septal defect (VSD)
 2. Right ventricular outflow tract obstruction (RVOTO)
 3. Aortic root “overriding” VSD
 4. Right ventricular hypertrophy
- See Figure 2, P20

Ebstein's Anomaly

- congenital defect of the tricuspid valve in which the septal and posterior leaflets are malformed and displaced into the RV leading to variable degrees of RV dysfunction, TS, TR or functional pulmonary atresia if RV unable to open pulmonic valves
- RA massively enlarged, interatrial communication patent foramen ovale (PFO) often exists allowing R → L shunting
- TR and accessory conduction pathways (WPW) are often present – often associated with arrhythmia
- cause: unknown, associated with maternal lithium and benzodiazepine use in 1st trimester
- treatment
 - in newborns, consider closure of tricuspid valve + aortopulmonary shunt, or transplantation
 - in older children, tricuspid valve repair or valve replacement + ASD closure

2. OTHER CYANOTIC CONGENITAL HEART DISEASES

Transposition of the Great Arteries (TGA)

- 3-5% of all congenital cardiac lesions, most common cyanotic CHD in neonate
- parallel pulmonary and systemic circulations
 - systemic: body → RA → RV → aorta → body
 - pulmonary: lungs → LA → LV → pulmonary artery → lungs
- physical exam
 - no murmur if no VSD
 - newborn presents with progressive cyanosis unresponsive to oxygen therapy as the ductus arteriosus closes and mixing between the two circulations diminishes; severe hypoxemia, acidosis, and death can occur rapidly
 - if VSD present, cyanosis is not prominent and infant presents with CHF after a few weeks of life
- investigations
 - ECG: RAD, RVH
 - CXR: egg-shaped heart with narrow mediastinum (“egg on a string”)
- treatment
 - prostaglandin E1 (Prostin VR®) infusion to keep ductus open until septostomy or surgery (arterial switch procedure)
 - infants without VSD must be repaired within 2 weeks to avoid weak LV muscle



Hypoplastic LHS
Hypoplastic LV
Narrow mitral/aortic valves
Small Ascending Aorta
Contracted Aorta

Hypoplastic Left Heart Syndrome

- 1-3% of all congenital cardiac lesions
- a spectrum of hypoplasia of left ventricle, atretic mitral and/or aortic valves, small ascending aorta, coarctation of the aorta with resultant systemic hypoperfusion
- most common cause of death from congenital heart disease in first month of life
- systemic circulation is dependent on ductus patency; upon closure of the ductus, infant presents with circulatory shock and metabolic acidosis
- treatment
 - intubate and correct metabolic acidosis
 - IV infusion of PGE1 to keep ductus open
 - surgical correction (overall survival 50% to late childhood) or heart transplant

Total Anomalous Pulmonary Venous Connection

- only 1-2% of CHD
- characterized by all of the pulmonary veins draining into the right-sided circulation (supracardiac – SVC or innominate vein, infracardiac – hepatic/portal vein or IVC, intracardiac – coronary sinus or RA)
- no direct oxygenated pulmonary venous return to left atrium
- often associated with obstruction at connection sites
- an ASD must be present to allow blood to shunt into the LA and systemic circulation
- treatment: surgical repair if severe cyanosis or CHF related to pulmonary venous obstruction

Truncus Arteriosus

- a single great vessel arising from the heart which gives rise to the aorta, pulmonary and coronary arteries
- the truncal valve overlies a large VSD
- treatment: surgical repair within first 6 months of life to prevent development of pulmonary vascular disease

Congestive Heart Failure (CHF)

- see Cardiology, C32

Etiology

- congenital heart disease (CHD)
- arteriovenous malformations (AVMs)
- cardiomyopathy
- arrhythmias
- acute hypertension
- anemia
- cor pulmonale
- myocarditis

Symptoms

- infant: feeding difficulties, easy fatigability, exertional dyspnea, diaphoresis when sleeping or eating, respiratory distress, lethargy, cyanosis, FTT
- child: decreased exercise tolerance, fatigue, decreased appetite, failure to thrive, respiratory distress, frequent URIs or “asthma” episodes
- orthopnea, paroxysmal nocturnal dyspnea, pedal/dependent edema are all NOT common in children

Physical Findings

- four key features: tachycardia, tachypnea, cardiomegaly, hepatomegaly
- failure to thrive (FTT)
- respiratory distress, gallop rhythm, wheezing, crackles, cyanosis, clubbing (with CHD)
- alterations in peripheral pulses, four limb blood pressures (in some CHDs)
- dysmorphic features associated with congenital syndromes
- CXR – cardiomegaly, pulmonary venous congestion

Management

- correction of underlying cause
- general: sitting up, O₂, sodium and water restriction, increased caloric intake
- pharmacologic: diuretics, digoxin, afterload reducers



4 Key Features of CHF
2 Tachy's and 2 Megaly's
 Tachycardia
 Tachypnea
 Cardiomegaly
 Hepatomegaly



Pharmacologic Management of CHF
3 D's
 Diuretics
 Digoxin
 Afterload Decreasers

Infective Endocarditis

- see [Infectious Diseases](#), ID14
- 70% *Streptococcus*, 20% *Staphylococcus* (*S. aureus*, *S. epidermidis*)
- serial positive cultures are needed for definitive diagnosis, but rely on clinical suspicion and other investigations if initially negative (i.e. use Echo to look for vegetations)
- 10-15% of cases are culture negative, this is a risk factor for poor prognosis
- Osler's nodes, Janeway's lesions, splinter hemorrhages are late findings in children
- antibiotic prophylaxis is necessary for all patients with:
 - cyanotic congenital heart disease (including Tetralogy of Fallot, TGA, Ebstein's anomaly, total anomalous pulmonary venous return)
 - rheumatic valve lesions (except if no valve dysfunction)
 - prosthetic heart valves
 - palliative shunts and conduits
 - previous endocarditis
 - pacemaker leads
- SBE prophylaxis: amoxicillin 50 mg/kg 30 to 60 minutes before procedure (if allergic to penicillin, then use clindamycin 20 mg/kg)
- high risk patients for GI/GU procedures may receive 2 doses amp + gent IV (30 min before procedure and 6 hours later)

Dysrhythmias

- see [Cardiology](#), C12
- can be transient or permanent, congenital (structurally normal or abnormal) or acquired (toxin, infection, infarction)

Sinus Arrhythmia

- phasic variations with respiration
- present in almost all normal children

Premature Atrial Contractions (PACs)

- may be normal variant or can be caused by electrolyte disturbances, hyperthyroidism, cardiac surgery, digitalis toxicity

Premature Ventricular Contractions (PVCs)

- common in adolescents
- benign if single, uniform, disappear with exercise, and no associated structural lesions
- if not benign, may degenerate into more severe dysrhythmias

Supraventricular Tachycardia (SVT)

- most frequent sustained dysrhythmia in children
- not life-threatening but can lead to symptoms
- caused by re-entry via accessory connection (atrioventricular (AV) node most common site)
- characterized by a rate of greater than 210 bpm
- treatment
 - stable (alert, normal BP)
 - ♦ vagal manoeuvres: apply cold to face, rectal stimulation, valsava
 - ♦ adenosine
 - ♦ synchronized cardioversion
 - unstable (decreased LOC, decreased BP)
 - ♦ immediate synchronized cardioversion

Complete Heart Block

- congenital heart block can be caused by maternal Rho or La antibody (e.g. in mothers with SLE)
- often diagnosed in utero – may lead to development of fetal hydrops
- clinical symptoms related to level of block (the lower the block, the greater the symptoms of inadequate cardiac output)
- symptomatic patients need a pacemaker



Pediatric vs. Adult ECG

Pediatric ECG findings that may be normal:

- HR > 100 bpm
- Shorter PR, QT intervals and QRS duration
- Inferior and lateral small Q waves
- RV larger than LV in neonates, so normal to have:
 - Right axis deviation
 - Large precordial R waves
 - Upright T waves

Development



Developmental Delay

- developmental delay is defined as performance significantly below average in a given area

Epidemiology

- 5-10% of children have neurodevelopmental delay
- may have isolated delays in specific areas (motor, speech/language), or global delays

Etiology

- genetic/chromosomal disorders (Down syndrome, Fragile X)
- intrapartum asphyxia
- CNS abnormalities (meningitis/encephalitis, TORCH infections, structural)
- metabolic disorders (inborn errors of metabolism, hypothyroidism)
- environmental (psychosocial neglect, lead exposure, antenatal drug or alcohol exposure)

Approach

- detailed history
 - intrauterine exposures, perinatal events
 - family history, consanguinity
 - detailed developmental milestones – rate of acquisition, regression of skills
 - associated problems (feeding, seizures, behaviour, sleep)
 - social history
- physical examination
 - dysmorphism, hepatosplenomegaly, neurocutaneous markers, growth parameters, detailed neurological examination
- ancillary testing
 - neurodevelopmental assessment, hearing test, psychosocial evaluation, occupational therapy and/or physiotherapy assessments, genetics consultation
- laboratory testing
 - target testing based on history and physical exam
 - chromosomes, FISH, neuroimaging, metabolic testing, neuroelectrophysiologic testing



Intellectual Disability

- also referred to as mental retardation

Epidemiology

- 1% of general population; M:F = 1.5:1
- higher rates of sensory deficits, motor impairment, behavioural/emotional disorders, seizures, psychiatric illness

Etiology

- genetic: Down syndrome, Fragile X, PKU, other chromosomal disorders, developmental brain abnormality, inborn errors of metabolism
- prenatal: rubella, fetal alcohol syndrome, prenatal exposure to heroin, cocaine, TORCH infections, HIV, maternal DM, toxemia, maternal malnutrition, birth trauma/hypoxia
- perinatal: prematurity, low birth weight, cerebral ischemia, intracranial hemorrhage, maternal deprivation
- childhood: intracranial infection, head trauma, FTT, lead poisoning
- psychosocial factors: mild mental retardation (MR) associated with low socioeconomic status (SES), limited parental education, parental neglect, teen pregnancy, family instability

Diagnosis

- below average general intellectual functioning as defined by an IQ of approximately 70 or below (2 standard deviations below the mean) AND
- deficits in adaptive functioning in at least two of:
 - communication, self-care, home-living, social skills, self-direction, academic skills, work, leisure, health, safety
- onset before 18 years of age

Table 14. Classification of Intellectual Disability

Severity	% Cases	IQ
Mild	85%	50-70
Moderate	10%	35-49
Severe	3-4%	20-34
Profound	1-2%	<20

Treatment

- main objective: enhance adaptive functioning level
- therapy
 - emphasize community-based treatment vs. institutionalization and early intervention
 - individual/family therapy, behaviour modification (to decrease aggressive/distracting behaviours), multidisciplinary rehabilitation, medications for associated conditions
- education: life skills, vocational training, communication skills, family education
- psychosocial support of parents and respite care

Language Delay

Differential Diagnosis

- hearing impairment
 - spectrum of impairment – slight to profound loss
 - language development may seem normal for up to 6 months (including cooing and babbling) but may regress due to lack of feedback
 - risk factors for sensorineural hearing loss (>1 risk factor warrants infant screening, if newborn screening not available in jurisdiction for all newborns):
 - ◆ genetic syndromes/family history
 - ◆ congenital (TORCH) infections
 - ◆ craniofacial abnormalities
 - ◆ <1,500 g birthweight
 - ◆ hyperbilirubinemia/kernicterus
 - ◆ asphyxia/low APGAR scores
 - ◆ bacterial meningitis, viral encephalitis
 - to evaluate hearing loss in children:
 - ◆ <6 months old: auditory brainstem response (ABR), tympanometry (impedance testing), evoked potentials
 - ◆ >6-8 months old: behaviour audiometry
 - ◆ >3-4 years old: pure tone audiometry
- cognitive disability
 - global developmental delay, mental retardation
 - both receptive and expressive language components affected
 - child often has interest in communication
- pervasive developmental disorder (PDD), including autism
 - poor social interaction and language impairment, stereotypical behaviours
- selective mutism
 - a childhood anxiety disorder with onset age 5-6
 - only speaks in certain situations, usually at home
 - healthy children with no hearing impairment
 - often above-average intelligence
- Landau-Kleffner syndrome (acquired epileptic aphasia)
 - presents in late preschool to early school age years, may be similar to autism
 - child begins to develop language normally, then sudden regression of language
 - child has severe aphasia with EEG changes, often has overt seizure activity
- mechanical problems
 - cleft palate
 - cranial nerve palsy
- social deprivation

Management

- ENT and dental referral if mechanical cause
- speech therapy in disorders of fluency, receptive or expressive language
- psychiatric consultation in selective mutism, PDD

Learning Disorders

Definition

- a specific and persistent failure to acquire academic skills despite conventional instruction, adequate intelligence, and sociocultural opportunity
- a significant discrepancy between a child's intellectual ability and his or her academic performance

Epidemiology

- prevalence: 2-10%
- psychiatric comorbidity = 10-25% of individuals with dysthymia, conduct disorder (CD), major depressive disorder (MDD), oppositional defiant disorder (ODD), attention deficit hyperactivity disorder (ADHD)

Diagnosis

- categorized by
 - individual scores on achievement tests in reading, mathematics or written expression (WISC III, WRAT) significantly below (>2 SD) that expected for age, education, and IQ
 - interferes with academic achievement or ADLs that require reading, mathematics, or writing skills
- types: reading, mathematics, disorders of written expression
- rule out occult seizure disorder, sensory impairments

Complications

- low self-esteem, poor social skills
- 40% school drop-out rate

Fetal Alcohol Spectrum Disorder (FASD)

Definition

- umbrella term describing the range of effects that can occur after prenatal exposure to alcohol
- effects may include physical, mental, behavioural and learning disabilities
- diagnoses included are Fetal Alcohol Syndrome (FAS), partial Fetal Alcohol Syndrome (pFAS), Alcohol-Related Birth Defects (ARBD), and Alcohol-Related Neurodevelopmental Disorder (ARND)
- not known how much alcohol is harmful during pregnancy

Epidemiology

- prevalence of FAS and FASD is 0.1 and 1.0% respectively
- most common preventable cause of intellectual disability

Diagnosis

- often misdiagnosed or missed entirely
- early diagnosis is essential to prevent secondary disabilities
- individuals with FASD and their families should be linked to community resources and services to improve outcome
- criteria for diagnosis of FAS (most severe form of FASD)
 - a) growth deficiency – low birth weight and/or decelerating weight over time not due to nutrition
 - b) characteristic pattern of facial anomalies – short palpebral fissures, flattened philtrum, thin upper lip, flat midface
 - c) central nervous system dysfunction – microcephaly and/or neurobehavioural dysfunction (e.g. hyperactivity, fine motor problems, attention deficits, learning disabilities, cognitive disabilities)
 - d) evidence of maternal drinking during pregnancy
- criteria for diagnosis of ARBD
 - a) congenital anomalies, including malformations and dysplasias – includes cardiac, skeletal, renal, ocular, auditory anomalies
 - b) evidence of maternal drinking during pregnancy
- criteria for diagnosis of ARND
 - a) central nervous system dysfunction (similar to FAS)
 - b) complex pattern of behavioural or cognitive abnormalities inconsistent with developmental level that cannot be explained by familial background or environment alone
 - c) evidence of maternal drinking during pregnancy

Complications

- secondary disabilities include unemployment, mental health problems, trouble with the law, inappropriate sexual behaviour, disrupted school experience, peer problems



No "safe" level of alcohol consumption during pregnancy has been established.

Endocrinology



Diabetes Mellitus (DM)

- see [Endocrinology](#), E6

TYPE 1 DIABETES (Insulin-Dependent DM)

Epidemiology

- insulin dependent, most common type in childhood
- prevalence: 1 in 400-500 children under 18 years of age
- can present at any age; bimodal peaks 5-7 years and puberty
- classic presentation: polyuria, polydipsia, abdominal pain, weight loss, and fatigue
- 25% present with diabetic ketoacidosis (DKA)

Etiology

- genetic predisposition and environmental trigger
 - autoimmune destruction of beta-cells of the pancreas (antibodies directed towards glutamic acid decarboxylase have been identified)
 - a non-immune variation has been described
 - diseases of pancreas (i.e. cystic fibrosis) and long term corticosteroids

Management of Uncomplicated Diabetes

- meal plan, exercise, education, psychosocial support
- insulin injections 2-3 times per day, blood glucose monitoring
- young children more susceptible to CNS damage with hypoglycemia with fewer benefits from tight control, hence target glucose range higher at 6-12 mmol/L (110-220 mg/dL)
- increasingly tighter control in older children, 4-8 mmol/L (70-140 mg/dL)
- continuous subcutaneous insulin infusion (CSII) pump
 - contains a cartridge full of short-acting insulin (Lispro®) or a syringe connected to a catheter that is inserted into the subcutaneous tissue
 - continuously delivers predetermined basal rates to meet nonprandial insulin requirements
 - bolus infusion to cover meal time or snack time insulin requirements
 - requires as much or more blood glucose monitoring when compared to injections ± ketone monitoring – patients must be highly motivated
 - allows for tighter glycemic control
 - risk of DKA with operator or mechanical failure (catheter occlusion, battery failure, depleted insulin)

Complications of Type 1 Diabetes

- hypoglycemia
 - cause: missed/delayed meals, excess insulin, increased exercise, illness
 - complications: seizures, coma
 - must have glucagon kit for quick injections
 - infants may not show classic catecholaminergic signs with hypoglycemia
- hyperglycemia
 - cause: infection, stress, diet-to-insulin mismatch, eating disorder
 - complications: risk of DKA, long-term end-organ damage
- DKA
 - cause: new-onset diabetes, missed insulin doses, infection
 - medical emergency: most common cause of death in children with diabetes (attributed to cerebral edema)
- long-term complications (retinopathy, nephropathy, neuropathy)
 - usually not seen in childhood (often begins 5 years after presentation or 3-5 years after puberty)
- metabolic syndrome
- other auto-immune conditions (e.g. celiac disease, hypothyroidism)

TYPE 2 DIABETES

- these tend to be obese and present with glycosuria without ketonuria, absent or mild polydipsia and polyuria, little weight loss
- especially prevalent among North American Aborigines, Africans, Asians, Hispanics
- onset age >10 and in middle to late puberty
- may present in DKA or hyperglycemic hyperosmotic nonketotic (HONK) states

Treatment

- ill child with ketosis – insulin
- well child without ketosis – diet, exercise, oral agents
- metformin is used in children because it does not cause hypoglycemia



Diagnostic Criteria for Diabetes Mellitus

Symptoms (polyuria, polydipsia, weight loss) + random glucose ≥ 11.1 mmol/L (200 mg/dL)

OR

Fasting glucose ≥ 7.0 mmol/L (126 mg/dL)

OR

2hr glucose during OGTT ≥ 11.1 mmol/L (200 mg/dL)

OGTT = oral glucose tolerance test



If a child presents with polyuria and polydipsia, dip urine for glucose and ketones.



Blood Glucose Targets by Age

Age range	Pre-meal blood glucose target	HbA1C target
<6	5.6-10.0 (100-180)	7.5-8.5%
6-12	5.0-10.0 (90-180)	<8%
>12	5.0-7.2 (90-130)	<7.5%

Diabetes Insipidus (DI)

- DI is the inability of the kidneys to concentrate urine
- central:
 - due to decreased ADH production from the brain (genetic, due to trauma, surgery, radiation, neoplasm, meningitis)
 - presents with polyuria, polydipsia, enuresis
- nephrogenic:
 - renal unresponsiveness to ADH (genetic, drug-induced)
 - X-linked recessive condition that affects males in early infancy
 - polyuria, FTT, hyperpyrexia, vomiting, hypernatremic dehydration

Diagnosis

- symptoms: polyuria, enuresis, nocturia, polydipsia, dehydration
- labs: dilute urine (SG <1.010), hypernatremia, elevated serum osmolality, low urine osmolality
- water deprivation test; central cause if >50% change in urine osmolality after ADH administration

Management

- central: DDAVP intranasally, SC or PO
- nephrogenic: low-solute diet, thiazide diuretics

Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

- etiology: intracranial, malignancy, pulmonary disease, psychiatric disease, drugs
- common in hospitalized patients (associated with post-op pain and nausea)
- symptoms: asymptomatic, oliguria, volume expansion, or hyponatremic symptoms (nausea, vomiting, H/A, seizure, coma)
- labs: hyponatremia, urine Osm > plasma Osm, urine Na >40 mmol/L
- management: fluid restriction, 3% NaCl for symptomatic hyponatremia

Hypercalcemia/Hypocalcemia/Rickets

- see [Endocrinology](#), E38, E40, E45

Hypothyroidism

- see [Endocrinology](#), E26

Congenital Hypothyroidism

- incidence: 1 in 4000 births; F:M=2:1
- usually caused by malformation of the thyroid gland (agenesis or ectopic), maternal factors also involved (iodine deficiency, prenatal exposure to antithyroid medications or radioiodine)
- diagnosis through newborn screening of TSH or T4
- usually asymptomatic in neonatal period because maternal T4 crosses the placenta but may have the following symptoms:
 - prolonged jaundice
 - constipation
 - sluggish, hoarse cry, lethargy, poor feeding
 - macroglossia, coarse facial features, large fontanelles, umbilical hernia
- prognosis
 - excellent if treatment started within 1-2 months of birth
 - if treatment started after 3-6 months of age may result in permanent developmental delay and/or mental retardation (mild to profound)
- management: thyroxine replacement

Acquired Hypothyroidism

- most commonly Hashimoto's thyroiditis (autoimmune destruction of the thyroid)
- signs and symptoms similar to hypothyroidism in adults, but also:
 - delayed bone age, decline in growth velocity, short stature, goiter
 - sexual pseudoprecocity: early sexual development with short stature and delayed bone age
 - does not cause permanent developmental delay
- treated with L-thyroxine 10 µg/kg/day



Thyroid neoplasms that develop in childhood have a higher rate of being malignant; be suspicious of rapid and painless enlargement of the thyroid gland.

Hyperthyroidism

- see [Endocrinology](#), E22

Congenital Hyperthyroidism

- results from transplacental passage of maternal thyroid stimulating antibodies (mother with Graves' disease)
- clinical manifestations may be masked if mother on antithyroid treatment
- presentation: tachycardia with congestive heart failure, irritability, craniosynostosis, poor feeding, failure to thrive, heart murmur, goitre
- spontaneous resolution by 2-3 months of life as antibodies cleared
- management: propylthiouracil until antibodies cleared, symptomatic treatment

Graves' Disease

- peak incidence in adolescence; F:M = 5:1
- may exhibit classic signs and symptoms of hyperthyroidism, especially ophthalmopathy, but also personality changes, school difficulty, mood instability
- management similar to adults: anti-thyroid drugs (propylthiouracil, methimazole), propranolol for severe/cardiac manifestation, radioiodine reserved for older teens, surgical thyroidectomy
- children with a solitary thyroid nodule require prompt evaluation as 30-40% have carcinoma; the remainder have an adenoma, abscess, cyst, or multinodular goiter

Ambiguous Genitalia

Etiology

- male pseudohermaphrodite (XY)
 - inborn error of testosterone biosynthesis or Leydig cell hypoplasia
 - 5-alpha-reductase deficiency, androgen receptor deficiency or insensitivity
 - luteinizing hormone (LH)/hCG unresponsiveness
 - small phallus, hypospadias, undescended testicles
- female pseudohermaphrodite (XX)
 - virilizing congenital adrenal hyperplasia (CAH) (most common)
 - maternal source: virilizing ovarian or adrenal tumours, untreated maternal CAH, placental aromatase deficiency
 - virilization of external genitalia – clitoral hypertrophy, labioscrotal fusion
- mixed pattern
- true hermaphrodite
 - both ovarian follicles and seminiferous tubules in the same patient with a 46XX karyotype
 - increased risk of malignant transformation of gonad tissue
- mixed gonadal dysgenesis

Investigations

- history: pregnancy (hormones and medications), family history
- physical exam: palpation of gonads, rectal exam (except in newborns)
- investigations
 - karyotype
 - electrolytes and renin (evidence of salt-wasting in CAH)
 - measurement of 17-OH-progesterone (must wait until day 3 of life), androgens, follicle stimulating hormone (FSH) and luteinizing hormone (LH)
 - abdominal U/S to look for uterus, testicles, ovaries

Clinical Presentation

- depends on the degree and the specific deficiency
- infants may present with FTT, shock, salt-wasting (adrenal crisis due to lack of aldosterone), hyperpigmentation (genital, areola), clitoral hypertrophy, fused labia
- hypertension is rare (usually seen in the 11-hydroxylase variant)
- adult onset (11-hydroxylase variant) more insidious, may present as hirsutism
- female: ambiguous genitalia to complete virilization, amenorrhea
- male: precocious puberty, with early adrenarche, dehydration
- accelerated linear bone growth in early years, but premature epiphyseal closure due to high testosterone, resulting in decreased adult height
- possible Addisonian picture (adrenal insufficiency) if adrenal output of cortisol severely compromised

Congenital Adrenal Hyperplasia (CAH)

- occurs in 1/15000 live births and is the most common cause of ambiguous genitalia
- autosomal recessive condition causing partial or total enzyme defect
- 21-hydroxylase deficiency causes 95% of CAH cases; this causes decreased cortisol and aldosterone with shunting toward overproduction of androgens
- cortisol deficiency leads to elevated ACTH, which causes adrenal hyperplasia
- clinical presentation depends on the specific deficiency and the cause – may present with shock, hyperkalemia if not suspected
- for steroid biosynthesis pathway, see [Endocrinology](#), E29



The salt-wasting form of CAH is a medical emergency – babies can die of vomiting, dehydration and shock at 2-4 weeks of age; order glucose and electrolytes; replace fluids and electrolytes, manage hypoglycemia, and start the child on lifelong hydrocortisone.

Salt-Wasting 21-Hydroxylase Deficiency (2/3 of cases)

- infants present with shock, FTT, low Na, high K, low Cl, low glucose, adrenal insufficiency, high ACTH
- hyperpigmentation of genitals and areola and postnatal virilization

Late-Onset 21-Hydroxylase Deficiency

- allelic variant of classic 21-hydroxylase deficiency – mild enzymatic defect
- girls present with amenorrhea
- boys present with precocious puberty with early adrenarche, dehydration
- accelerated linear growth in early puberty but early fusion of epiphyses leading to decreased adult height
- diagnosis
 - increased plasma 17-OH-progesterone after ACTH stimulation test
- treatment
 - dexamethasone, spironolactone (anti-androgen)
 - mineralocorticoid replacement is not needed

Simple Virilizing 21-Hydroxylase Deficiency

- virilization in girls but not boys

11-Hydroxylase Deficiency

- sexual ambiguity in females
- may have insidious onset; may present with hirsutism, occasionally hypertension

17-Hydroxylase Deficiency

- sexual ambiguity in males, hypertension

Investigations

- low Na, high K, low cortisol, high ACTH if both glucocorticoid and mineralocorticoid deficiency
- increased serum 17-OH-progesterone (substrate for 21-hydroxylase)
- increased testosterone, DHEAS, urinary 17-ketosteroids
- advanced bone age

Treatment

- glucocorticoid replacement to lower ACTH
- in salt-wasting type mineralocorticoids given as well
- spironolactone is used in late-onset 21-hydroxylase deficiency as anti-androgen
- surgery to correct ambiguous genitalia

Table 15. Clinical Features of CAH Based on Enzyme Defect

Enzyme Defect	Sexual Ambiguity		Postnatal Virilization	Salt Wasting	Hypertension
	Female	Male			
21-hydroxylase					
salt-wasting	–	–	+	+	–
simple virilizing	+	–	+	–	–
late onset	–	–	+	–	–
11-hydroxylase	+	–	+	–	+
17-hydroxylase	–	+	–	–	+

Precocious Puberty

- secondary sexual development <8 years in girls, <9 years in boys
 - incidence: 1 in 10,000
 - more common in females; more worrisome in males (higher incidence of pathology)
- indications for medical intervention to delay progression of puberty are male sex, age <6, bone age advancing more quickly than height age, and psychological issues
- GnRH agonists such as leuprolide are most effective at delaying central precocious puberty
- medications used in peripheral precocious puberty include ketoconazole (to block steroid production), 5- α reductase blockers (finasteride), steroid receptor blockers (spironolactone), aromatase blockers (testolactone, anastrozole)

True (Central) Precocious Puberty

- hypergonadotropic hypergonadism, hormone levels as in normal puberty
- premature activation of the hypothalamic-pituitary-gonadal axis
- much more common in females than males – 9:1
- differential diagnosis
 - idiopathic or constitutional (most common, especially females)
 - CNS disturbances: tumours, hamartomas, post-meningitis, increased ICP, radiotherapy
 - neurofibromatosis (NF), primary severe hypothyroidism



A child with proven central precocious puberty should receive an MRI of the brain.

Pseudo (Peripheral) Precocious Puberty

- hypogonadotropic hypergonadism
- differential diagnosis
 - adrenal disorders: CAH, adrenal neoplasm
 - testicular/ovarian tumour
 - gonadotropin secreting tumour: hepatoblastoma, intracranial teratoma, germinoma
 - exogenous steroid administration
 - McCune-Albright syndrome: endocrine dysfunction resulting in precocious puberty, café-au-lait spots, and fibrous dysplasia of skeletal system

Investigations

- history: symptoms of puberty, family history of puberty onset, medical illness
- physical exam: growth velocity, Tanner staging, neurological exam
- estradiol, testosterone, LH, FSH, TSH, GnRH test
- bone age (often advanced)
- consider CT or MRI of head, U/S of adrenals, pelvis

Treatment

- GnRH analogs, GnRH agonist (Lupron®) – negative feedback to downregulate GnRH receptors
- medroxyprogesterone – slows breast and genital development
- treat underlying cause

Contrasexual Precocious Puberty

- development of secondary sexual characteristics opposite to genotypic sex
- e.g. virilizing tumour (ovarian, adrenal), CAH, exogenous androgen exposure

Delayed Puberty

- absence of pubertal development by age 13 in girls and age 14 in boys
- more common in males, more suggestive of pathology in females

Central Causes

- delay in activation of hypothalamic-pituitary-gonadal axis
- hypogonadotropic hypogonadism
- differential diagnosis
 - constitutional (bone age delayed) – most common (>90%)

Peripheral Causes

- hypergonadotropic hypogonadism (e.g. primary gonadal failure)
- differential diagnosis
 - genetic (e.g. Turner syndrome, Klinefelter's syndrome)
 - gonadal damage – infection, radiation, trauma
 - gonadal dysgenesis
 - hormonal defect – androgen insensitivity, 5-alpha-reductase deficiency

Investigations

- history: weight loss, short stature, family history of puberty onset, medical illness
- physical exam: growth velocity (minimum 4 cm/year), Tanner staging, neurological exam, complete physical exam
- hormone levels: estradiol, testosterone, LH, FSH, TSH, GnRH, test bone age
- consider CT or MRI of head, ultrasound of adrenals, pelvis
- karyotype in girls <3rd percentile in height (rule out Turner syndrome)

Management

- identify and treat underlying cause
- hormonal replacement: cyclic estradiol and progesterone for females, testosterone for males

Short Stature



Short Stature DDX

ABCDEFGF

- A**lone (neglected infant)
- B**one dysplasias (rickets, scoliosis, mucopolysaccharidoses)
- C**hromosomal (Turner, Down)
- D**elayed growth
- E**ndocrine (low growth hormone, Cushing, hypothyroid)
- F**amilial
- G**I malabsorption (celiac, Crohn's)



4 Questions to Ask when Evaluating Short Stature

1. Was there IUGR?
2. Is the growth proportionate?
3. Is the growth velocity normal?
4. Is bone age delayed?

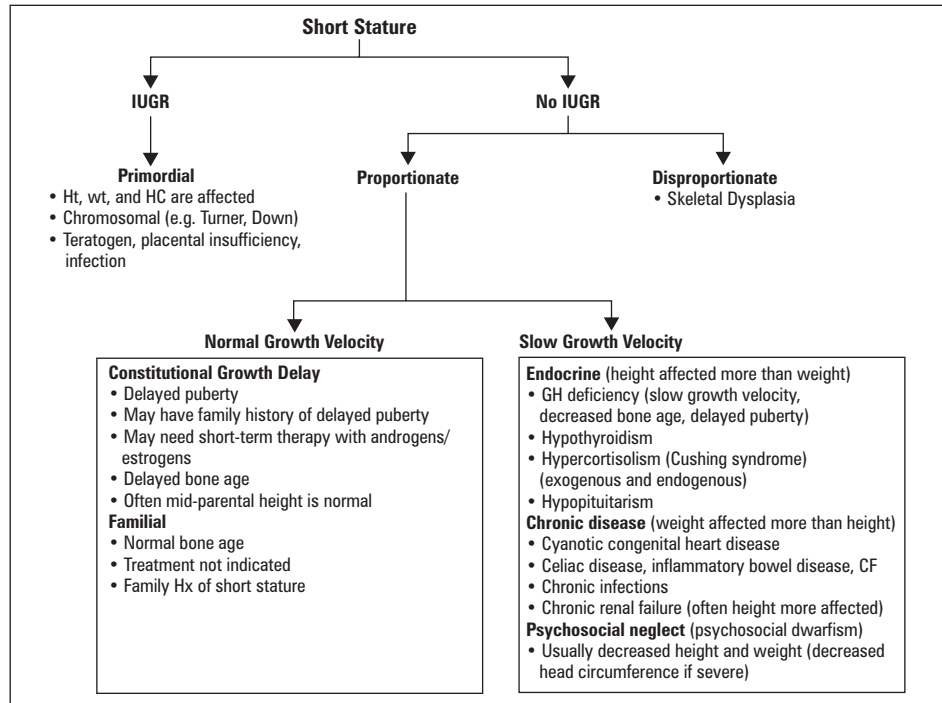


Figure 3. Approach to the Child with Short Stature

- special growth charts available for Turner syndrome, achondroplasia, Down syndrome (DS); growth velocity is often normal
- children are usually in a percentile between their parents' height
- decreased growth velocity may be more worrisome than actual height

Assessment of Short Stature

- height <3rd percentile, height crosses 2 major percentile lines, low growth velocity (<25th percentile)
- history: perinatal history, growth pattern, medical history, parental height and age of pubertal growth spurt
- physical exam: growth velocity (over 6 month period), sexual development
- growth hormone (GH) deficiency accounts for a small minority of children with short stature

Investigations

- bone age (anteroposterior x-ray of left hand and wrist)
- karyotype in girls to rule out Turner syndrome or if dysmorphic features present
- other tests as indicated by history and physical exam

Management

- depends on severity of problem as perceived by parents/child
- no treatment for non-pathological short stature
- GH therapy if requirements met (see *Growth Hormone Deficiency*, P35)



Calculate mid-parental height (predicted adult height) \pm 8 cm for 2 SD ranges

- Check the mid-parental height for percentile of adults
- Boy = [father height (cm) + mother height (cm) + 13 cm]/2
- Girl = [father height (cm) + mother height (cm) - 13 cm]/2

Growth Hormone (GH) Deficiency

- GH important for chondrocyte proliferation and IGF-1 release
- GH has little effect on fetal growth (maternal IGF-1, uterine factors more important)
- IGF-1 acts at long bones, liver, negative feedback

Etiology

- congenital GH deficiency
 - idiopathic
 - embryologic CNS malformation: associated midface anomalies, neurologic defects, micropenis in males and hypoglycemia
 - perinatal asphyxia
 - rare mutations
- acquired GH deficiency
- tumours (e.g. craniopharyngioma), trauma, cranial infection, irradiation, post-surgical

Clinical Presentation

- infantile features and fat distribution (short and chubby), delayed puberty, hypoglycemia, high-pitched voice

Investigations

- testing for GH deficiency (stimulation testing) only performed when:
 - height <3rd percentile
 - decreased growth velocity
 - midline craniofacial anomalies
 - episodes of hypoglycemia
 - delayed bone age, puberty
- physiologic increase in GH with: arginine, clonidine, insulin, dopamine, or propranolol
- positive test if failure to raise GH >8-10 ng/mL post-stimulation

Treatment

- GH therapy indicated if:
 - GH shown to be deficient by 2 different stimulation tests
 - short stature, insufficient growth velocity, <3rd percentile
 - bone age x-rays show unfused epiphyses
 - Turner syndrome, Noonan syndrome, chronic renal failure

Tall Stature

- constitutional tall stature: advanced height and bone age during childhood but not necessarily associated with tall adult height (obesity can contribute to this by causing bone age to advance more rapidly)

Etiology

- constitutional/familial: most common, advanced bone age/physical development in childhood but normal once adulthood reached
- endocrine: hypophyseal (pituitary) gigantism, precocious puberty, thyrotoxicosis, Beckwith-Wiedemann syndrome
- genetic: Marfan syndrome, Klinefelter's syndrome, Sotos syndrome, homocystinuria

Investigations

- history and physical examination: differentiate familial from other causes
- calculate mid-parental height (predicted adult height, see sidebar P34)
- look for associated abnormalities (e.g. hyperextensible joints, long fingers in Marfan syndrome)

Treatment

- depends on etiology
- treatment only required in pituitary gigantism
- estrogen used in females to cause epiphyseal fusion (rarely indicated)

Gastroenterology

Vomiting



Vomiting: forceful expulsion of stomach contents through the mouth.

Regurgitation: the return of partially digested food from the stomach to the mouth.

- investigations (based on history and physical exam)
 - bloody emesis: investigate for causes of upper gastrointestinal (GI) bleed
 - bilious emesis: rule out obstruction (upper GI series, U/S)
 - evaluate for gastroesophageal reflux (24-hour esophageal pH probe)
 - CBC, electrolytes, BUN, creatinine, ESR, venous blood gases, amylase, lipase
 - urine, blood, stool C&S
 - abdominal x-ray, U/S, contrast radiology, endoscopy
 - consider head imaging
- management
 - rehydration (see *Pediatric Nephrology*, P76)
 - treat underlying cause



Vomiting in the Newborn Period

Tracheoesophageal Fistula (TEF)

- incidence: 1:3,000-1:4,500
- clinical presentation (vary with type of fistula)
 - may have history of maternal polyhydramnios
 - may present after several months (if no associated esophageal atresia), with vomiting, coughing, and gagging
 - cyanosis with feeds, respiratory distress, recurrent pneumonia
 - frothy bubbles of mucus in mouth and nose that return after suctioning
 - associated anomalies in 50%: VACTERL association (see *Pediatric Genetics, Dysmorphisms and Metabolism*, P47)
 - x-ray: anatomic abnormalities, NG tube curled in pouch
- management
 - investigate for other congenital anomalies
 - early repair by surgical ligation to prevent lung damage and maintain nutrition and growth
- complications
 - pneumonia, sepsis, reactive airways disease
 - following repair: esophageal stenosis and strictures at repair site, gastroesophageal reflux and poor swallowing (i.e. dysphagia, regurgitation)

Pyloric Stenosis

- incidence: 1:500, M:F = 4:1, onset common in first-born males, positive FHx
- clinical features
 - non-bilious projectile vomiting that occurs after feeding
 - usually starts at 2-4 weeks of age
 - infant hungry and alert, will re-feed
 - constipation, FTT, wasting
 - dehydration, may lead to prolonged jaundice
 - gastric peristalsis goes from left upper quadrant (LUQ) to epigastrium
 - "olive sign": olive-shaped mass at margin of right rectus abdominus muscle
 - hypochloremic metabolic alkalosis
- diagnosis: clinical, abdominal U/S and x-ray
- treatment: surgical (pyloromyotomy)

Duodenal Atresia

- incidence: 1:10 000, 50% are born prematurely
- clinical features
 - bile-stained vomiting if atresia distal to bile duct
 - no abdominal distention
 - dehydration
 - associated with Down syndrome, prematurity
 - often have history of maternal polyhydramnios
- abdominal x-ray: air-fluid levels on upright film; "double bubble" sign (dilated stomach and duodenum)
- differential diagnosis: annular pancreas, aberrant mesenteric vessels, pyloric stenosis
- treatment
 - decompression with NG tube, correction of metabolic abnormalities, surgical correction



Pyloric Stenosis 3 P's

Palpable mass

Peristalsis visible

Projectile vomiting (2-4 weeks after birth)

Malrotation of the Intestine

- incidence: 1:500, symptomatic 1:6000
- 80% experience symptoms in first two months of life
- 3 presentations
 - recurrent vomiting (bilious intermittently)
 - FTT with vomiting
 - sudden onset abdominal pain and then shock (if vomiting with bilious material, suspect malrotation with volvulus until proven otherwise)
- clinical features
 - distended abdomen
 - vomiting due to volvulus and bands across duodenum
- diagnosis: abdominal U/S and upper GI series
- treatment: NG tube decompression and surgery
- complications: volvulus is a surgical emergency as it can result in bowel perforation, peritonitis, and bowel necrosis

Vomiting After the Newborn Period**Infectious and Inflammatory**

- GI causes: gastroenteritis, peritonitis, appendicitis, hepatitis, ulcers, pancreatitis, cholecystitis
- non-GI causes: urinary tract infection (UTI), pyelonephritis, nephrolithiasis, otitis media, labyrinthitis, meningitis, pneumonia

Anatomic

- GI tract obstruction: intussusception, volvulus, foreign body (e.g. bezoar)

Gastroesophageal Reflux

- extremely common in infancy (up to 50%): thriving baby requires no investigation
- vomiting typically soon after feeding, non-bilious, rarely contains blood, small volume (<1 oz)
- investigations required if: FTT, recurrent cough, pneumonia or bronchospasm, GI blood loss, symptoms persist after 18 months
 - 24-hour pH probe, UGI series to rule out anatomical cause, upper endoscopy and esophageal biopsy for suspected esophagitis
- management
 - conservative: thickened feeds, frequent and smaller feeds, elevate bed to 45°
 - medical:
 - ♦ short-term parenteral feeding to enhance weight gain
 - ♦ ranitidine, omeprazole: to decrease gastric acidity, decrease esophageal irritation
 - ♦ domperidone: to improve gastric emptying and GI motility
 - surgical: indicated for failure of medical therapy (Nissen fundoplication)
- complications: esophagitis, strictures, Barrett's esophagus, FTT, aspiration

Central Nervous System

- increased intracranial pressure (ICP) (e.g. hydrocephalus, neoplasm)
- drugs/toxins
- migraine, cyclic vomiting

Other

- metabolic/endocrine: DKA, inborn errors of metabolism, liver failure
- poisons/drugs: lead, digoxin, erythromycin, theophylline
- psychogenic: rumination syndrome, anorexia/bulimia
- food allergy
- overfeeding
- pregnancy

Acute Diarrhea**Table 16. Causes of Acute Diarrhea**

Infectious			Non-Infectious
Viral	Bacterial	Parasitic	Antibiotic-induced
Rotavirus	<i>Salmonella</i>	<i>Giardia lamblia</i>	Non-specific: associated with systemic infection
Norwalk	<i>Campylobacter</i>	<i>Entamoeba histolytica</i>	Hirschsprung's disease
Enteric Adenovirus	<i>Shigella</i>		Toxin ingestion
	Pathogenic <i>E. coli</i>		Primary disaccharide deficiency
	<i>Yersinia</i>		
	<i>C. difficile</i>		



Diarrhea is defined as an increase in frequency and/or decreased consistency of stools compared to normal.
 Normal stool volume:
 Infants: 5-10 g/kg
 Children: 200 g/day

VIRAL INFECTION

- most common cause of gastroenteritis in Canada and worldwide
- rotaviruses are the most common agent, often seen in winter months in temperate climates
- astroviruses are the second most important etiological agent, common in both developing and developed nations
- Norwalk virus is the third most common agent; typically affects older children and adults
- clinical features
 - associated with URIs
 - resolves in 3-7 days
 - slight fever, malaise, vomiting, vague abdominal pain

BACTERIAL INFECTION

- clinical features: severe abdominal pain, high fever, bloody diarrhea
- risk factors: travel, poorly cooked meat, poorly refrigerated foods

**Indications for Medical Evaluation of Acute Diarrhea**

- Age <6 months
- Fever
- Visible blood in stool
- Frequent, substantial volume of diarrhea
- Signs of dehydration
- Change in mental status

MMWR Recomm Rep 2003; 52 (RR-16):1-16

Investigations

- history and physical examination critical to determine degree of dehydration (see *Pediatric Nephrology*, P76)
- rectal exam for fecal consistency and for microscopy (leukocytes suggestive of invading pathogen)
- stool for culture and sensitivity (C&S), ova and parasites (O&P), electron microscopy for viruses
- if severe: routine blood work, blood and urine cultures

Treatment

- prevention and treatment of dehydration is most important (see *Dehydration*, P76)
- oral rehydration therapy with frequent small volumes of pediatric rehydration solutions, IV may be required (see *Fluid and Electrolyte Therapy*, P76)
- early refeeding advisable, start with small amounts of easily digested carbohydrates, postpone dairy and fibrous vegetables
- antibiotic therapy when indicated, antidiarrheal medications not indicated
- notify Public Health authorities if appropriate

**Chronic Diarrhea****Investigations**

- perform serial heights, weights, growth percentiles
- if child is growing well and thriving, minimal workup is required
- investigations depending on suspected diagnosis
 - stool: consistency, pH, reducing substances, microscopy, occult blood, O&P, C&S, *C. difficile* toxin, 3-day fecal fat
 - urinalysis
 - CBC, differential, ESR, smear, electrolytes, total protein, albumin
 - absorptive and nutritional status: albumin, carotene, Ca, PO₄, Mg, Fe, ferritin, folate, fat-soluble vitamins, PTT, INR
 - sweat chloride, thyroid function tests, urine vanillyl mandelic acid (VMA) and homovanillic acid (HVA), HIV test, lead levels
 - CXR, upper GI series and follow-through
 - specialized tests: endoscopy, small bowel biopsy



Chronic diarrhea: three or more loose, watery stools per day, lasting > 14 days.

**4F's Diet for Chronic Diarrhea**

Adequate Fibre
Normal Fluid intake
35-40% Fat
Discourage excess Fruit juice

Table 17. Causes of Chronic Diarrhea

0-3 months	3 months-3 years	3 years-18 years	Uncommon Causes
GI infection	Toddler's diarrhea	GI infection	Constipation with overflow diarrhea
Disaccharidase deficiency	GI infection	Celiac disease	Drug induced
Cow's milk intolerance	Celiac disease	IBD	UTI
Cystic fibrosis			Short bowel syndrome

**Chronic Diarrhea Without Failure to Thrive****Infectious**

- bacterial: *Campylobacter*, *Salmonella*
- antibiotic-induced: *C. difficile* colitis
- parasitic: *Giardia lamblia*
- post-infectious: secondary lactase deficiency

Toddler's Diarrhea

- epidemiology
 - most common cause of chronic diarrhea during infancy
 - onset between 6-36 months of age, ceases spontaneously between 2-4 years
- clinical presentation
 - diagnosis of exclusion in thriving child (no weight loss/FTT, no fluid or electrolyte abnormalities)
 - diet history: e.g. excess juice intake overwhelms small bowel resulting in disaccharide malabsorption
 - stool may contain undigested food particles, 4-6 bowel movements (BM's) per day
 - excoriated diaper rash
- management
 - reassurance, self-limiting
 - four F's (adequate Fibre, normal Fluid intake, 35-40% Fat, discourage excess Fruit juice)

Lactase Deficiency (Lactose Intolerance)

- clinical features
 - chronic, watery diarrhea
 - abdominal pain, bloating associated with dairy intake
- primary lactose intolerance: crampy abdominal pain with loose stool (older children, usually of East Asian and African descent)
- secondary lactose intolerance: older infant, persistent diarrhea (post viral/bacterial infection, celiac disease, or IBD)
- diagnosis
 - trial of lactose-free diet
 - watery stool, acid pH, positive reducing sugars
 - positive breath hydrogen test if >6 years
- management
 - lactose-free diet, soy formula
 - lactase-containing tablets/capsules/drops (e.g. Lacteeze®, Lactaid®)

Irritable Bowel Syndrome

- diagnosis of exclusion in older child/adolescent; may be similar to recurrent abdominal pain
- management
 - encourage high fibre diet
 - reassurance
 - medications (cAMP inhibitors) for refractory cases

Chronic Diarrhea With Failure to Thrive

**1. INTESTINAL CAUSES****Celiac Disease** (see Gastroenterology, G18)

- 1 in 300-500 incidence
- also known as "gluten-sensitive enteropathy", caused by a reaction to gliadin (a gluten protein)
- T-cell-mediated inflammation → damage to enterocytes
- defect in mucosa: immune-mediated inflammation and destruction of absorptive villi
- clinical features
 - presents at any age, usually 6-24 months with the introduction of gluten in the diet
 - FTT with poor appetite, irritability, apathy
 - anorexia, nausea, vomiting, edema, anemia, abdominal pain
 - wasted muscles, distended abdomen, flat buttocks, clubbing of fingers
 - rickets
 - non-GI manifestations: dermatitis herpetiformis, dental enamel hypoplasia, osteopenia/osteoporosis, short stature, delayed puberty
 - associated with other auto-immune disorders
- diagnosis
 - anti-transglutaminase (tTG), antigliadin, antiendomysial antibodies (anti-EMA), low D-xylose absorption
 - fat malabsorption studies
 - small bowel biopsy (gold standard): total villous atrophy with resolution after trial of gluten-free diet
- treatment
 - gluten-free diet for life
- complications if untreated
 - small bowel lymphoma
 - malnutrition, FTT



Celiac disease diet must avoid gluten present in "BROW" foods
 Barley
 Rye
 Oats (controversial)
 Wheat



Celiac disease is associated with an increased prevalence of IgA deficiency. Since tTG is an IgA-detecting test, you must order an accompanying IgA level.

Milk Protein Allergy

- immune-mediated mucosal injury
- up to 50% of children intolerant to cow's milk may be intolerant to soy protein as well
- often history of atopy
- 2 scenarios
 - enterocolitis: vomiting, diarrhea, anemia, hematochezia
 - enteropathy: chronic diarrhea, hypoalbuminemia
- treatment: casein hydrosylate formula (dairy-free e.g. Nutramigen®, Pregestimil®)

Inflammatory Bowel Disease (IBD) (see *Gastroenterology*, G36)

- incidence: 15-30:100 000, increasing in North America, mostly older children and teenagers

Other GI Causes

- specific enzyme deficiencies
- liver disease, biliary atresia
- alpha-beta-lipoproteinemia
- short gut toxic or immunologic reaction
- blind loop syndrome
- giardiasis

2. PANCREATIC INSUFFICIENCY**Cystic Fibrosis (CF)** (see *Pediatric Respiriology*, P94)**Schwachman-Diamond Syndrome**

- incidence: 1:20,000, autosomal recessive
- pancreatic insufficiency, cyclic neutropenia, and anemia
- skeletal abnormalities (metaphyseal dysostosis leading to short stature)
- recurrent pyogenic infections
- distinguished from CF by normal sweat chloride test, characteristic metaphyseal lesions, fatty pancreas on CT

3. OTHER

- diets rich in sorbitol, fructose (poorly absorbed carbohydrates)
- metabolic/endocrine
 - thyrotoxicosis, Addison's disease, galactosemia
- immune defects
 - IgA deficiency, hypogammaglobulinemia, severe combined immunodeficiency (SCID), AIDS
- neoplastic
- pheochromocytoma, lymphoma of small bowel, carcinoid tumours, secretory tumours
- food allergy
- laxative abuse

**Constipation****Functional Constipation**

- 99% of cases of constipation
- lack of fibre in diet or change in diet, poor fluid intake
- infants: often when introducing cow's milk after breast milk because increased fat and solute amounts, lower water content
- toddlers/older children: can occur during toilet training, or due to pain on defecation, stool withholding
- complications
 - pain retention cycle: anal fissures and pain → withhold passing stool → chronic dilatation and overflow incontinence
- treatment
 - adequate fluid intake (if <6 months, 150 ml/kg/day)
 - adequate dietary fibre, mineral oil, gentle laxatives occasionally (chronic use not recommended)
 - appropriate toilet training technique

Hirschsprung's Disease (congenital aganglionic megacolon)

- failure of normal innervation of the distal colon by the ganglion cells of the myenteric plexus
- colon remains contracted and impairs fecal movement
- incidence: M:F = 3:1; 1 in 5,000 live births
- clinical features
 - typically only rectosigmoid involvement but may extend to entire colon
 - no meconium within first 24 hours
 - palpable stool on abdominal exam with empty rectum on digital rectal exam
 - intermittent diarrhea, BM only with rectal stimulation
 - constipation, abdominal distention, vomiting, failure to thrive

**Constipation**

Decreased stool frequency (<3 stools/week) and/or stool fluidity.



As many as 20% of children <5 years of age experience constipation.

- complications
 - enterocolitis: may be fatal, peak incidence 2-3 months of age
 - toxic megacolon and perforation
- diagnosis
 - abdominal x-ray – cannot see gas in rectum
 - barium enema: proximal dilatation due to functional obstruction, empty rectum
 - manometric studies: shows failure of anal sphincter relaxation, may have false positives
 - rectal biopsy: definitive diagnosis (absent ganglion cells)
- treatment
 - nonsurgical if short segment: increase fibre and fluid intake, mineral oil
 - surgical: colostomy and re-anastomosis

Other Organic Disorders Causing Constipation

- endocrine: hypothyroidism, diabetes mellitus (DM), hypercalcemia
- neurologic: spina bifida
- anatomic: bowel obstruction, anus (imperforate, atresia, stenosis)
- drugs: lead, chemotherapy, opioids

Current Recommended Treatments of Childhood Constipation are Not Evidence Based: A Systematic Literature Review on the Effect of Laxative Treatment and Dietary Measures
Arch Dis Child 2009; 94:117-131
Study: Systematic review of studies assessing the effect of medical and dietary treatment of functional constipation.
Patients: 37 included publications, a total of 1912 children with constipation.
Intervention: PEG vs. placebo, vs. lactulose, and vs. other laxatives; Lactulose vs. other laxatives; Senna; Mineral oil; Fibre; etc.
Outcome: Defecation frequency.
Results: No clinically significant difference between laxatives, and between fibre vs. placebo; although most studies failed to compare laxatives to placebo. There was greater treatment success with PEG as compared to all other laxatives.

Acute Abdominal Pain

Table 18. Differential Diagnosis for Acute Abdominal Pain

Gastrointestinal	Other Systems
Gastroenteritis, malabsorption	UTI
Incarcerated hernia, intussusception	Henoch-Schönlein Purpura (HSP)
Appendicitis, Meckel's diverticulitis	Sickle cell crisis
Malrotation, volvulus	Pneumonia
IBS, mesenteric adenitis	DKA
Cholecystitis, pancreatitis	Nephrolithiasis
Somatization	Gynecological (ectopic pregnancy, PID, endometriosis, menstruation)

Assessment

- description of pain (location, radiation, duration, constant vs. colicky, relation to meals)
- associated symptoms: nausea, vomiting, diarrhea, fever
- physical examination: peritoneal signs, bowel sounds, rectal exam
- labs: CBC, differential, urinalysis to rule out urinary tract infection (UTI)

Appendicitis

- see *General Surgery*, GS27
- most common cause of acute abdomen after 5 years of age
- clinical features
 - low grade fever, anorexia
 - nausea, vomiting (after onset of pain)
 - abdominal pain, peritoneal signs
 - generalized peritonitis is a common presentation in infants/young children
- treatment: surgical
- complications: perforation, abscess

Intussusception

- 90% idiopathic, children with CF or GJ tube at significantly increased risk
- 50% between 3-12 months, 75% before 2 years of age
- telescoping of segment of bowel into distal segment → ischemia and necrosis
- usual site: ileocecal junction; jejunum in children with GJ tubes
- lead point of telescoping segment may be swollen Peyer's patches, Meckel's diverticulum, polyp, malignancy, Henoch-Schönlein Purpura
- clinical features
 - "classic triad"
 - ◆ abdominal pain
 - ◆ palpable sausage-shaped mass: upper to mid-abdomen
 - ◆ "red currant jelly" stools (only in 10-15% of patients)
 - sudden onset of recurrent, paroxysmal, severe periumbilical pain with pain-free intervals
 - later vomiting and rectal bleeding
 - shock and dehydration
- diagnosis and treatment
 - U/S
 - air enema diagnostic, can be therapeutic (reduce intussusception in 75% of cases)
 - reduction under hydrostatic pressure
 - surgery rarely needed



Intussusception – Classic Triad
 Abdominal pain
 Palpable mass
 Red currant jelly stools

**Chronic Abdominal Pain****Rule of 3's**

- 3 episodes of severe pain
- Child >3 years old
- Over 3 month period

**Red Flags for Organic Etiology of Chronic Abdominal Pain**

- Age <5 years old
- Fever
- Localizes pain away from midline
- Anemia
- Rectal bleeding
- Rash
- Pain awakens child at night
- Travel history
- Prominent vomiting, diarrhea
- Weight loss or failure to gain weight
- Joint pain



Chronic Abdominal Pain

- 10-15% of children
- definition "rule of 3s" = 3 episodes of pain severe enough to affect activities, occurring in a child >3 years of age over a period of 3 months
- distinguish organic from non-organic

Organic (<10%)

- gastrointestinal
 - constipation (cause vs. effect), infectious
 - IBD, esophagitis, peptic ulcer disease, lactose intolerance
 - anatomic anomalies, masses
 - pancreatic, hepatobiliary
- genitourinary causes
 - recurrent urinary tract infections, nephrolithiasis, chronic PID, mittelschmerz
- neoplastic

Functional/Recurrent Abdominal Pain (RAP) (90%)

- school age, peak 8-10 years
- prevalence: 10% of school children, F>M
- characteristics
 - vague, crampy periumbilical or epigastric pain, vivid imagery to describe pain, clustering of episodes
 - seldom awakens child from sleep
 - aggravated by exercise, alleviated by rest
- psychological factors related to onset and/or maintenance of pain, school avoidance
- psychiatric comorbidity: anxiety, somatoform, mood, learning disorders, sexual abuse, eating disorders, elimination disorders
- diagnosis by exclusion of organic disorders
- investigations as indicated
 - CBC, ESR, urinalysis, stools for O&P, C&S, occult blood
- treatment
 - continue to attend school
 - manage any emotional or family problems, counselling
 - trial of high fibre diet, trial of lactose-free diet
 - reassurance
- prognosis
 - pain resolves in 30-50% of kids within 2-6 weeks of diagnosis
 - 30-50% of kids with RAP have functional pain as adults (e.g. irritable bowel syndrome)

Abdominal Mass

Table 19. Differential Diagnosis for Abdominal Mass

	Benign	Malignant
Renal	Hydronephrosis Polycystic kidney disease (PCKD) Hamartoma	Nephroblastoma (Wilms) Renal cell carcinoma (RCC)
Adrenal		Neuroblastoma
Ovarian	Ovarian cysts	Ovarian tumours
Other	Splenomegaly Pyloric stenosis Abdominal hernia Teratoma Fecal impaction	Lymphoma Rhabdomyosarcoma Retroperitoneal sarcoma

- 50% of abdominal masses in the newborn are renal in origin

Upper Gastrointestinal Bleeding

- see Gastroenterology, G26

Lower Gastrointestinal Bleeding

- see Gastroenterology, G28

ETIOLOGY

Acute

- infectious (bacterial, parasitic)
- antibiotic-induced (*C. difficile*)
- necrotizing enterocolitis in preterm infants
- anatomic
 - malrotation/volvulus, intussusception
 - Meckel's diverticulitis
 - anal fissures, hemorrhoids
- vascular/hematologic
 - Henoch-Schönlein Purpura (HSP)
 - hemolytic uremic syndrome (HUS)
 - coagulopathy

Chronic

- anal fissures (most common)
- colitis
- inflammatory bowel disease (IBD)
- allergic (milk protein)
- structural
 - polyps (most are hamartomas)
 - neoplasms (rare)
- coagulopathy

Assessment

- hemodynamic status, evidence of FTT, fever
- anal and rectal exam
 - tags, fissures, anal fistulas, polyps
 - foreign body
 - blood
 - stool appearance
- NG aspirate
 - lower GI bleed may present as melena (if it involves the small bowel) or hematochezia
- stool cultures (*C. difficile*)
- urinalysis and microscopy
- CBC, smear, differential, platelets, ESR, electrolytes, urea, creatinine, INR, PTT, albumin, iron studies, amoeba titers
- radiologic investigations
 - abdominal x-ray (AXR) to rule out obstruction

Treatment

- acute stabilization: ABCs, volume and blood replacement, bowel rest (NPO, NG tube)
- once stable, endoscopy and surgery as indicated

Genetics, Dysmorphisms and Metabolism

- minor anomaly: an unusual anatomic feature that is of no serious medical or cosmetic consequence to the patients
- major anomaly
 - 1°
 - ♦ malformation – results from an intrinsically abnormal developmental process (e.g. polydactyly)
 - 2°
 - ♦ disruption – results from the extrinsic breakdown of, or an interference with, an originally normal developmental process (e.g. amniotic band disruption sequence)
 - ♦ deformation – results from mechanical forces (e.g. Potter deformation sequence)

Mendelian Inheritance

- disorders caused by mutation of one or both copies of a gene, inherited in one of several patterns
 - autosomal – encoded by genes on one of 22 pairs of autosomes
 - ♦ autosomal dominant (AD) = disorder is expressed in a heterozygote (inheritance is 'vertical', both males and females are affected and can transmit the trait); e.g. neurofibromatosis type I
 - ♦ autosomal recessive (AR) = disorder is manifest only in homozygotes (inheritance is 'horizontal', disease not found in multiple generations, parents of an affected child are usually normal); e.g. cystic fibrosis



Definitions

Association: non-random concurrence of independent malformations whose etiology is unknown (e.g. VACTERL association).

Sequence: pattern of multiple anomalies derived from a single known or presumed prior anomaly or mechanical factor (e.g. oligohydramnios sequence).

Syndrome: recognized pattern of developmentally independent malformations having one known etiology (e.g. Down syndrome).

- X-linked – encoded by a gene on the X chromosome
 - ♦ males have a single X chromosome and are affected, females have two X chromosomes, and recessive X-linked disorders are rarely expressed in females; e.g. Duchenne Muscular Dystrophy (DMD)

Approach to the Dysmorphic Child

- 2-3% of infants are born with a serious congenital defect, 1% have a monogenetic disease, 0.5% have a chromosomal disorder and 1-3% have a multifactorial illness
- genetic disorders are the most common cause of infant death in developed countries
- diagnosis of syndromes is based on pattern of dysmorphic features and organ involvement

History

- prenatal/obstetrical history (see *Obstetrics*)
- complete 3 generation family pedigree: consanguinity, stillbirths, neonatal deaths, specific illnesses, intellectual disability, multiple miscarriages, ethnicity

Physical Examination

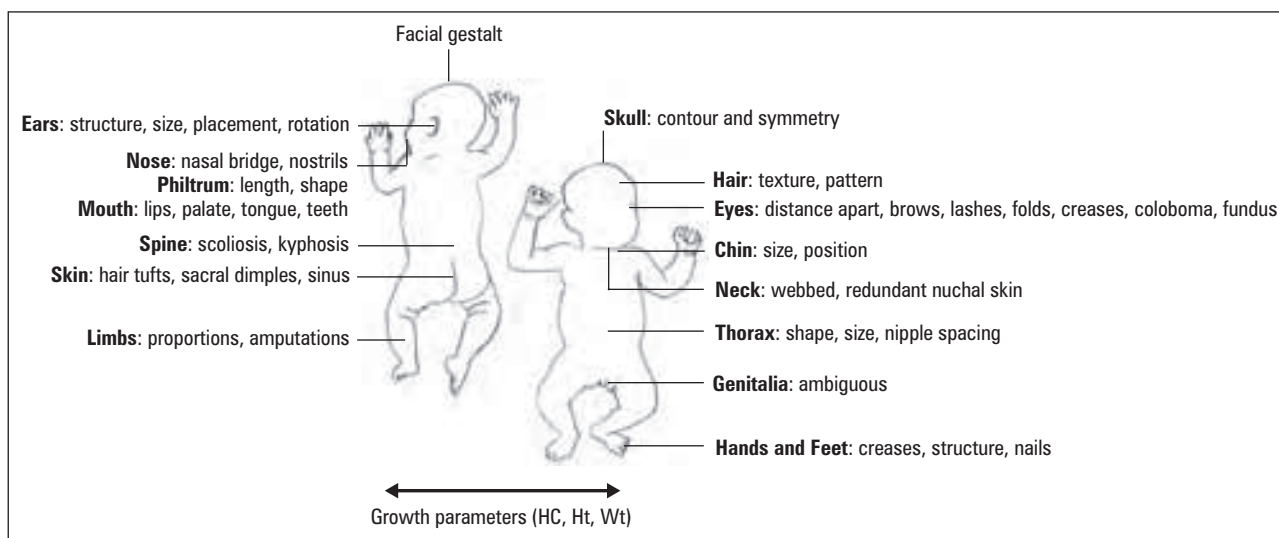


Figure 4. Physical Examination of the Dysmorphic Child

Investigations

- ask for serial photographs if child is older or family pictures
- x-rays if bony abnormalities or if suspect a congenital infection
- cytogenetic/chromosome studies ± skin fibroblasts
- biochemistry: specific enzyme assays
- genetic probes, e.g. Fragile X, microdeletion 22
- prenatal counselling and assessing risk of recurrence
- skin fibroblasts if mosaicism suspected

Genetic Syndromes

Table 20. Common Genetic Syndromes

	Trisomy 21	Trisomy 18	Trisomy 13
Disease	Down syndrome	Edwards syndrome	Patau syndrome
Incidence	1:600-800 births Most common abnormality of autosomal chromosomes Rises with advanced maternal age from 1:2000 at age 20 to 1:20 by age 45	1:6000 live births Female:male = 3:1	1:10 000 live births
Cranium/brain	Mild microcephaly, flat occiput, 3rd fontanelle, brachycephaly	Microcephaly, prominent occiput	Microcephaly, sloping forehead, occipital scalp defect, holoprosencephaly
Eyes	Upslanting palpebral fissures, inner epicanthal folds, speckled iris (Brushfield spots), refractive errors (myopia), acquired cataracts, nystagmus, strabismus	Microphthalmia, hypotelorism, iris coloboma, retinal anomalies	Microphthalmia, corneal abnormalities
Ears	Low-set, small, overfolded upper helix, frequent AOM, hearing loss	Low-set, malformed	Low-set, malformed

Table 20. Common Genetic Syndromes (continued)

	Trisomy 21	Trisomy 18	Trisomy 13
Facial Features	Protruding tongue, large cheeks, low flat nasal bridge, small nose	Cleft lip/palate Small mouth, micrognathia	60-80% cleft lip and palate
Skeletal/MSK	Short stature Excess nuchal skin Joint hyperflexibility (80%) including dysplastic hips, vertebral anomalies, atlantoaxial instability	Short stature Clenched fist with overlapping digits, hypoplastic nails, clinodactyly, polydactyly	Severe growth retardation Polydactyly, clenched hand
Cardiac defect	40%, particularly AVSD	60% (VSD, PDA, ASD)	80% (VSD, PDA, ASD)
GI	Duodenal/esophageal/anal atresia, TE fistula, Hirschsprung disease, chronic constipation	Hernia	
GU	Cryptorchidism, rarely fertile	Polycystic kidneys, cryptorchidism	Polycystic kidneys
CNS	Hypotonia at birth Low IQ, developmental delay, hearing problems Onset of Alzheimer's disease in 40's	Hypertonia	Hypo- or hypertonia Seizures, deafness Severe developmental delay
Other features	Simian (transverse palmar) crease, clinodactyly and absent middle phalanx of the 5th finger 1% lifetime risk of leukemia Polycythemia Hypothyroidism	Small for gestational age (SGA) Rocker-bottom feet	Single umbilical artery Midline anomalies: scalp, pituitary, palate, heart, umbilicus, anus
Prognosis/Management	Prognosis: long-term management Recommend chromosomal analysis Echo, thyroid test, atlanto-occipital x-ray at 2 years, hearing test, ophthalmology assessment Early intervention programs help children reach full potential	44% die in 1st month 10% survive past 1 year (profound intellectual disability in survivors)	33% die in 1st month, 50% by 2nd month, 90% by 1 year from FTT Profound intellectual disability in survivors

Table 21. Most Common Sex Chromosome Disorders

	Fragile X Syndrome	Klinefelter's Syndrome	Turner Syndrome	Noonan Syndrome
Genotype	X-linked Genetic anticipation CGG trinucleotide repeat on X chromosome confers easy breakage of chromosome	47 XXY (most common) 48XXXY, 49XXXXY	45X (most common) Mosaic: 46XX with p deletion, 45X0/47XXX	46XX or 46XY Autosomal dominant (not a sex chromosome disorder) with variable expression Higher transmission of affected maternal gene
Incidence	1:3600 males, 1:6000 females Most common genetic cause of intellectual disability in boys	1:1000 live male births Increased risk with advanced maternal age	1:4000 live female births Risk not increased with advanced maternal age	1:2000 male and female live births
Phenotype	Overgrowth: Prominent jaw, forehead, and nasal bridge with long and thin face, large protuberant ears, macroorchidism, hyperextensibility, and high arched palate Complications: Seizures, scoliosis, mitral valve prolapse	Tall, slim, underweight No features prepuberty Postpuberty: male may suffer from developmental delay, long limbs, gynecomastia, lack of facial hair	Short stature, short webbed neck, low posterior hair line, wide carrying angle Broad chest, widely spaced nipples Lymphedema of hands and/or feet, cystic hygroma in newborn with polyhydramnios, lung hypoplasia Coarctation of aorta, bicuspid aortic valve Renal and cardiovascular abnormalities, increased risk of HTN Less severe spectrum with mosaic	Certain phenotypic features similar to females with Turner syndrome; therefore, sometimes called the "male Turner syndrome", although it affects both males and females Short stature, webbed neck, triangular facies, hypertelorism, low set ears, epicanthal folds, ptosis Pectus excavatum Right-sided congenital heart disease, pulmonary stenosis
IQ and Behaviour	Mild to moderate intellectual disability, 20% of affected males have normal IQ ADHD and/or autism Female carriers may show intellectual impairment	Mild intellectual disability Behavioural or psychiatric disorders – anxiety, shyness, aggressive behaviour, antisocial acts	Mildly deficient to normal intelligence	Moderate intellectual disability in 25% of patients
Gonad and Reproductive Function		Infertility due to hypogonadism/hyperpermia	Streak ovaries with deficient follicles, infertility, primary amenorrhea, impaired development of secondary sexual characteristics	Delayed puberty
Diagnosis/Prognosis/Management	Diagnosis: Cytogenetic studies: region on Xq which fails to condense during mitosis, fragile X marker Molecular testing: overamplification of the trinucleotide repeat, length of segment is proportional to severity of clinical phenotype (genetic anticipation)	Management: Testosterone in adolescence	Normal life expectancy if no complications Increased risk of X-linked diseases Management: Echo, ECG to screen for cardiac malformation GH therapy for short stature Estrogen replacement at time of puberty for development of secondary sexual characteristics	Management: Affected males may require testosterone replacement therapy at puberty Echo, ECG

Table 22. Other Genetic Syndromes

	DiGeorge Syndrome	Prader-Willi Syndrome	Angelman Syndrome	CHARGE Syndrome
Genotype	Microdeletions of 22q11	Lack of paternally imprinted genes on chromosome 15q11 Due to deletion of paternal chromosome 15q11 or two maternal chromosome 15s (maternal uniparental disomy)	Lack of maternally imprinted genes on chromosome 15q11	2/3 of children with CHARGE have been found to have the CHD7 mutation on chromosome 8
Incidence	Second most common genetic diagnosis (next to Down syndrome)	1:15 000		1:10 000
Clinical Features	"CATCH 22" C yanotic CHD (may account for up to 5% of all cases of CHD) A nomalies: craniofacial anomalies typically micrognathia and low set ears T hymic hypoplasia "immunodeficiency" recurrent infections C ognitive impairment H ypoparathyroidism, hypocalcemia 22q11 microdeletions	"H₂O": Hypotonia and weakness, Hypogonadism, O bsessive H yperphagia, O besity Short stature, almond-shaped eyes, small hands and feet with tapering of fingers Development delay (variable) Hypopigmentation, DM II	Severe intellectual disability, seizures, tremulousness, hypotonia Midface hypoplasia, fair hair, uncontrollable laughter	"CHARGE" C oloboma H congenital Heart disease A choanal Atresia R mental Retardation G GU anomalies E Ear anomalies

Muscular Dystrophy (MD)

- a group of inherited diseases characterized by progressive skeletal and cardiac muscle degeneration

Duchenne Muscular Dystrophy (DMD)

- 1:4000 males, 1/3 spontaneous mutations, 2/3 X-linked recessive
- missing structural protein dystrophin → muscle fibre fragility → fibre breakdown → necrosis and regeneration
- clinical features
 - proximal muscle weakness by age 3, positive Gower's sign (i.e. child uses hands to "climb up" the legs to move from a sitting to a standing position), waddling gait, toe walking
 - hypertrophy of calf muscles and wasting of thigh muscles
 - decreased reflexes
 - dystrophin is expressed in the brain, and boys with DMD may have delayed motor and cognitive development; this is not progressive
 - cardiomyopathy
 - moderate intellectual compromise
- diagnosis
 - family history (pedigree analysis)
 - increased CK (50-100x normal) and lactate dehydrogenase
 - muscle biopsy, electromyography (EMG)
- complications
 - patient usually wheelchair-bound by 12 years of age
 - early flexion contractures, scoliosis, develop osteopenia of immobility, increased risk of fracture
 - death due to pneumonia/respiratory failure or CHF in 2nd-3rd decade
- treatment
 - supportive (e.g. physiotherapy, wheelchairs, braces), prevent obesity
 - surgical (for scoliosis)
 - use of steroids (e.g. prednisone or deflazacort)
 - gene therapy trials underway

Becker's Muscular Dystrophy

- X-linked recessive, due to a mutation in dystrophin gene with some protein production
- symptoms similar to Duchenne but onset is later in childhood and progression is slower
- death due to respiratory failure in 4th decade

Associations

- associations are a non-random occurrence of multiple malformations with unknown etiology, while syndromes are a pattern of anomalies that have a known etiology
- **VACTERL** should be suspected when a child is found to have tracheo-esophageal fistula:
 - V** Vertebral dysgenesis (70%)
 - A** Anal atresia (imperforate anus) \pm fistula (80%)
 - C** Cardiac anomalies, such as VSD (53%)
 - T-E** TracheoEsophageal fistula \pm esophageal atresia (70%)
 - R** Renal anomalies (53%)
 - L** Limb anomalies, i.e. radial dysplasia, pre-axial polydactyly, syndactyly (65%)
 - may also present with a single umbilical artery or FTT
 - prognosis: may have normal health and mental development with aggressive treatment of abnormalities

Metabolic Disease

- an inherited disorder of intermediary metabolism; often autosomal recessive
- infants and older children may present with failure to thrive (FTT) or developmental delay
- currently in Canada and the United States, newborns may be tested for CAH, congenital hypothyroidism, galactosemia, sickle cell disease (in certain ethnic groups), PKU, maple syrup urine disease, homocystinuria, and biotinidase deficiency
- types of disorders
 - proteins: PKU, tyrosinemia, organic acid disorders, urea cycle defects
 - carbohydrates: galactosemia, glycogen storage diseases
 - fats: fatty acid oxidation defects
 - organelle disorders: congenital disorders of glycosylation, mucopolysaccharidosis

Clinical Manifestations

- vomiting and acidosis after feeding initiation (amino acid or carbohydrate metabolic disorder)
- hepatosplenomegaly (metabolites accumulate in the liver)
- neurologic syndrome: acute and chronic encephalopathy, intellectual disability, megalencephaly (mucopolysaccharide disorders)
- severe acidosis (aminoaciduria), hyperammonemia (urea cycle and organic acid disorders)
- growth retardation, seizures, coma, hypoglycemia
- autonomic manifestations (e.g. pallor, sweating, tremor)



Metabolic disease must be ruled out in any newborn who becomes acutely ill after a period of normal behaviour and development or with a family history of early infant death.

Physical Exam

- odour: burnt sugar, sweaty feet, musty, ammonia-like
- skin: hypo/hyperpigmentation, rash, xanthomas
- hair: alopecia, hirsutism, abnormal architecture, fair colouring
- eyes: cornea (clouding, crystals), lens (cataracts, dislocation), retina (macular cherry red spot, pigment retinopathy, optic atrophy)

Initial Investigations

- electrolytes, ABGs (calculate anion gap, rule out acidosis)
- CBC with differential and smear
- blood glucose (hypoglycemia seen with organic acidemia, fatty acid oxidation defects and glycogen storage diseases)
- lactate, ammonium (hyperammonemia with urea cycle defects), plasma Ca and Mg
- routine urinalysis: ketonuria must be investigated
- others: urate, urine nitroprusside, amino acid screen, CSF glycine, free fatty acids (3-beta-hydroxybutyrate ratio >4 in fatty acid oxidation defect)
- storage diseases: urine mucopolysaccharide and oligosaccharide screen

Phenylketonuria (PKU)

- incidence: 1 in 10 000
- screened in all newborns
- etiology: deficiency of phenylalanine hydroxylase prevents conversion of phenylalanine to tyrosine leading to build up of toxic metabolites
- mothers who have PKU may have infants with congenital abnormalities
- presentation
 - baby is normal at birth, then develops a musty odour, eczema, hypertonia, tremors, and mental retardation
 - hypopigmentation due to low tyrosine (fair hair, blue eyes)
- treatment
 - PKU screening at birth
 - dietary restriction of phenylalanine starting within the first 10 days of life
 - duration of dietary restriction controversial – lifelong or until end of puberty; should be resumed during pregnancy to maintain normal phenylalanine levels

Galactosemia

- incidence: 1 in 60 000, autosomal recessive disease
- most commonly due to deficiency of galactose-1-phosphate uridyltransferase leading to an inability to process lactose/galactose
- increased risk of sepsis
- if the diagnosis is not made at birth, liver and brain damage may become irreversible
- features: neonate who ingests lactose/galactose exhibits signs of liver and renal failure, jaundice, FTT and cataracts
- treatment
 - elimination of galactose from the diet (e.g. dairy, breast milk)
 - most infants are fed a soy-based diet



Hematology

Physiologic Anemia

- high hemoglobin (>170 g/L) and reticulocyte count at birth as a result of relatively hypoxic environment in utero
- after birth, levels start to fall due to shorter fetal RBC lifespan, decreased RBC production (during first 6-8 weeks of life, virtually no erythropoiesis due to new O₂ rich environment), and increasing blood volume secondary to growth
- lowest levels about 100 g/L at 8-12 weeks age (earlier and more exaggerated in premature infants); levels rise spontaneously with activation of erythropoiesis
- no treatment usually required



Normal Hg Values by Age

Age	Hg Range (g/L)
Newborn	137-201
2 weeks	130-200
3 months	95-145
6 months-6 years	105-140
7-12 years	110-160
Adult female	120-160
Adult male	140-180



MCV in childhood varies with age
Rule of thumb: lower normal limit of
MCV = 70 + age(yrs) until 80 fl (adult standard).

Iron Deficiency Anemia

- most common cause of childhood anemia
- full term infants exhaust iron reserves by 6 months age
- preterm infants have lower reserves, therefore exhausted by 2-3 months of age
- common diagnosis between 6 months-3 years and 11-17 years due to periods of rapid growth and increased iron requirements; adolescents also have poor diet and menstrual losses
- can cause irreversible effects on development if untreated (behavioural and intellectual deficiencies) in infancy
- presentation: usually asymptomatic until marked anemia, pallor, fatigue, pica (eating non-food materials), tachycardia, systolic murmur
- complications: angular cheilitis, glossitis, koilonychia

Etiology

- dietary risk factors
 - “milk baby” – baby (9-24 months old) receiving large volumes (>20 oz per day) of cow’s milk usually by bottle leading to poor intake of iron-rich foods
 - formula without iron
 - delayed introduction of iron fortified infant cereal
- blood loss
 - iatrogenic: repeated blood sampling (especially in hospitalized neonates)
 - true cow’s milk protein allergy: occult bleeding and protein-losing enteropathy secondary to GI inflammation



Iron deficiency is rare in children
<6 months in the absence of blood loss or prematurity.

Investigations

- CBC: low MCV and MCH, reticulocyte count normal or high (absolute number low), normal WBC
- Mentzer index (MCV/RBC) can help distinguish iron deficiency anemia from thalassemia
 - ratio <13 suggests of thalassemia; ratio >13 suggests iron deficiency
- blood smear: hypochromic, microcytic RBCs, pencil shaped cells, poikilocytosis
- iron studies: low ferritin, low iron, high TIBC
- initial therapy: trial of iron



Ferritin is an acute phase reactant, therefore, normal or high ferritin does not exclude iron deficiency anemia during an infection.

Prevention

- breastfed full-term infants: after 6 months, give iron-fortified cereals and iron-rich foods
- non-breastfed infants: give iron-fortified formula from birth
- premature infants: give iron supplements from 1 month to 1 year of age

Management

- encourage diverse, balanced diet, limit homogenized milk to 16-20 oz/day
- oral iron therapy – 6 mg/kg/day elemental iron, divided BID to TID, for 3 months to replete iron stores
 - increased reticulocyte count in 2-3 days (peaks day 5-7)
 - increased hemoglobin in 4-30 days
 - repletion of iron stores in 1-3 months
 - re-check hemoglobin levels after 1 month of treatment
- poor response to oral iron therapy: non-compliance, ongoing blood loss, incorrect diagnosis, insufficient duration of therapy, high gastric pH (antacid use)

Anemia of Chronic Disease

- most often normocytic, normochromic (microcytic, hypochromic may occur with chronic infection/malignancy)
- multi factorial in origin
- chronic inflammatory states including juvenile idiopathic arthritis (JIA), chronic infections, chronic renal failure, and malignancies
- iron stores are variable and ferritin levels are unreliable (acute phase reactant) therefore bone marrow assessment may be necessary for diagnosis
- anemia of chronic renal failure predominantly caused by decreased EPO production
 - treatment with erythropoietin

Hemoglobinopathies**SICKLE CELL DISEASE**

- see [Hematology](#), H19
- identification of specific genotypes important due to differences in frequency, type and severity of clinical complications (most severe: SS, less severe: SC, S-beta thalassemia, rare: SD). Also important for genetic counselling.

Pathophysiology

- caused by a genetic defect in beta-globin genes
 - HgS: single amino acid replacement (glutamic acid → valine)
- red blood cells sickle under conditions of stress (low pO₂, dehydration, fever, acidosis)
- acute intravascular sickling results in infarction of tissue (capillary occlusion and thrombosis of spleen, lungs, bones, brain, digits)
- hemolysis causes chronic, well-compensated, normochromic normocytic anemia (Hb 60-90 g/L)
- increased incidence in people of African and Mediterranean heritage
- greatest cause of mortality is infection



8% of African Americans carry the HbS trait, 0.2% have the disease. Heterozygotes (trait) are relatively malaria resistant.

Presentation

- newborns from high-risk families undergo screening; may be part of provincial newborn screening program
- clinical disease presents after 5-6 months of age after fall in fetal Hb
- anemia, fever, jaundice, splenomegaly, crisis (dactylitis is often the first presentation)
- sickle cell trait: asymptomatic (may have microscopic hematuria)

Types of Crises

- vaso-occlusive crisis
 - due to obstruction of blood vessels by rigid, sickled cells → tissue hypoxia → cell death; presents as fever and pain in any organ; most commonly in long bones of arms and legs, chest, abdomen, CNS (stroke), dactylitis (in young children), priapism
 - acute chest crisis: fever, chest pain, progressive respiratory distress, increased WBC count, pulmonary infiltrates
- aplastic crisis – depression of erythropoiesis (decreased reticulocyte count to <1%, decreased Hb), generally associated with infection (especially parvovirus B19)
- acute splenic sequestration – sudden, massive pooling of red cells in spleen, splenomegaly, tender spleen, acute fall in hemoglobin, shock, increased reticulocyte count

Functional Asplenia

- splenic dysfunction usually by 5 years of age secondary to autoinfarction
- susceptible to infection by encapsulated organisms (especially *S. pneumoniae*)
- requires prophylactic antibiotics, pneumococcal/meningococcal/*H. influenzae* type b vaccination, and immediate evaluation of any fever

Other Manifestations

- increased incidence of osteomyelitis (especially due to *Salmonella*)
- long term complications: growth delay, bony abnormalities – e.g. avascular necrosis (AVN) of femoral head, gallstones, retinopathy, restrictive lung disease (screen with PFTs), cardiomyopathy (screen with echo)

Management

- acute crises
 - admit for supportive and symptomatic treatment
 - fluids (1.5x maintenance; 1x maintenance only if in chest crisis), analgesia (morphine, multimodal), antibiotics (e.g. 3rd generation cephalosporins), incentive spirometry to decrease risk of chest crisis
 - straight transfusions for symptomatic/significant anemia (e.g. aplastic crisis), evolving chest crisis
 - RBC exchange transfusion for impending stroke, severe chest crisis, persistent priapism
 - O₂ if respiratory distress or chest crisis (with incentive spirometry)
 - cultures and CBC if febrile, reticulocyte counts, CXR or LP if indicated
- chronic
 - early aggressive treatment of infections, prophylactic antibiotics (daily oral penicillin)
 - pneumococcal, meningococcal, hepatitis B, Hib, and influenza vaccines
 - folate supplementation if folate deficient
 - hydroxyurea if frequent crises (raises HbF level)
 - transcranial doppler ultrasound to assess risk of stroke
 - chronic transfusion program if history of stroke or abnormal transcranial doppler
 - genetic counselling and education
 - annual ophthalmologic exam (after 10 years old)
 - referral to hematology

HEREDITARY SPHEROCYTOSIS

- red cell membrane protein abnormality; causes a spherizing of RBCs which are removed by the spleen
- genetics
 - autosomal dominant (positive family history in 75%)
 - high spontaneous mutation rate (no family history in 25%)
- wide range of clinical severity from well-compensated, mild hemolytic anemia to severe hemolytic anemia with growth failure, splenomegaly, gallstones, neonatal jaundice, and chronic transfusion requirements in infancy
- diagnosis: spherocytes (circular RBCs) on blood smear, osmotic fragility test
- management
 - transfusion, splenectomy as indicated
 - genetic counselling



G6PD deficiency protects against parasitism of RBCs (i.e. malaria).

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

- X-linked recessive; the most common enzyme deficiency worldwide
- higher prevalence in Mediterraneans, African Americans, Asians
- enzyme-deficient RBC unable to defend against oxidative stress (infection, drugs) → form Heinz bodies (Hb precipitates within RBCs) → phagocytosed by splenic macrophages creating “bite cells” (RBCs that appear to have bites taken out of them; also known as “cookie cells”)
- presents with acute hemolytic anemia (hemoglobinuria, decreased haptoglobin, increased LDH, and elevated indirect bilirubin) with jaundice, pallor and dark urine (rarely causes chronic anemia)
- diagnosis: G6PD enzyme assay
- management: supportive, hydration, transfusion, phototherapy
- prevention: avoid known oxidants e.g. fava beans, antimalarials (primaquine), sulfonamides

Bleeding Disorders

- see Hematology, H29

Coagulation Defects

- characterized by bleeding into joints (hemarthroses) and muscles
- large spreading ecchymoses and hematomas

Platelet Abnormalities

- characterized by petechiae, purpura, bruises, mucocutaneous bleeding (e.g. epistaxis, gingival bleeding), menorrhagia, prolonged bleeding from superficial cuts

Table 23. Classification of Bleeding Disorders

Site of Pathophysiology	Mechanism	Examples
Blood Vessels	Vasculitis	Henoch-Schönlein purpura
Platelets	Decreased production Increased destruction Increased consumption Dysfunctional	Drugs, marrow infiltration, leukemia/lymphoma Immune thrombocytopenic purpura, infection, drugs DIC, giant hemangioma, hypersplenism von Willebrand disease, drugs (ASA), uremia
Coagulation Pathway	Vitamin K deficiency Factor VIII deficiency Factor IX deficiency Abnormal vWF	Hemorrhagic disease of the newborn Hemophilia A Hemophilia B von Willebrand disease

Immune Thrombocytopenic Purpura (ITP)

- most common cause of thrombocytopenia in childhood
- peak age: 2-6 years, M=F
- incidence 5 in 100,000 children per year
- caused by antibodies that bind to platelet membranes → splenic uptake (Fc-receptor mediated) → destruction of platelets
- presentation and course
 - 50% present 1-3 weeks after viral illness (URTI, chicken pox)
 - sudden onset of petechiae, purpura, epistaxis in an otherwise well child
 - no lymphadenopathy, no hepatosplenomegaly
 - labs: thrombocytopenia with normal RBC, WBC
 - if atypical presentation (≥ 1 cell line abnormal, hepatosplenomegaly), do bone marrow to rule out leukemia
 - differential diagnosis: leukemia, drug-induced thrombocytopenia, HIV, infection (viral), SLE
 - highest risk of bleeding in first 1-2 weeks
- management
 - self-limited in children; spontaneous recovery in >80% of cases
 - usually choose to treat because spontaneous recovery takes a few months and there is increased risk of bleeding (especially intracranial hemorrhage with platelets <20)
 - IVIG or oral prednisone (mainstays of treatment), IV anti-D (if blood group Rh positive)
 - splenectomy (only for life-threatening bleeding)
 - avoid ASA/NSAIDs
 - no contact sports
 - reassurance: very low risk of serious hemorrhage (3%) and CNS hemorrhage rare (<0.5%)

Hemophilia

- see [Hematology](#), H29

von Willebrand's Disease

- see [Hematology](#), H28

Table 24. Evaluation of Abnormal Bruising/Bleeding

	BT	PT	PTT	VIII:C	vWF	Platelets	Fibrinogen
Hemophilia A	N	N	↑	↓	N	N	N
Hemophilia B	N	N	↑	N	N	N	N
von Willebrand's	↑	N	N or ↑	↓	↓	N	N
DIC	N or ↑	↑	↑	↓	N	↓	↓
Vitamin K Deficiency	N	↑	↑	N	N	N	N
Thrombocytopenia	↑	N	N	N	N	↓	N

BT = Bleeding Time, VIII:C = Factor VIII Coagulant Activity, vWF = von Willebrand's Factor, DIC = Disseminated Intravascular Coagulation

Corticosteroids versus Intravenous Immune Globulin for the Treatment of Acute Immune Thrombocytopenic Purpura in Children: A Systematic Review and Meta-analysis of Randomized Controlled Trials

J Pediatr 2005; 147(4):521-7

Study: Meta-analysis of 10 RCTs from 1985-2003. RCTs compared corticosteroids and IVIG in the treatment of pediatric ITP, and had to include patient platelet counts.

Patients: 586 children 3 months to 18 years of age who were presenting for the first time with primary acute ITP, with no other underlying condition.

Intervention: Corticosteroids and IVIG at any dose. Corticosteroid treatments included methylprednisolone 10-30 g/kg/d and prednisone 2-4 g/kg/d. IVIG dosing ranged from 0.5-1 g/kg/d. Treatment durations ranged from 1-5 days.

Main Outcome: Primary outcome was platelet levels > 20,000/mm³ (20x10⁹/L) at 48 hours after treatment. (This outcome was chosen because intracranial hemorrhage rarely occurs at platelet above 20). Secondary outcomes included incidence of ICH.

Results: The relative risk (RR) of reaching a platelet count > 20,000/mm³ at 48 hours was 0.74 (95%CI 0.65-0.85) for corticosteroids versus IVIG (at any dose), with a NNT of 4.55 (95%CI 3.23-7.69).

Subgroup analyses by dosing favoured IVIG in 6/10 dose comparisons. Only 3/586 children developed ICH – two were treated with corticosteroids and one with IVIG.

Summary: Children treated with corticosteroids are less likely to have a platelet count > 20,000/mm³ than children treated with IVIG after 48 hours of therapy. However, optimal dosing of IVIG is unclear, and impact of IVIG versus corticosteroids on ICH and mortality are unclear.



Extensive bruising in the absence of lab abnormalities: consider child abuse.



Rochester Criteria – developed to identify infants ≤60 days of age with fever at low risk of serious bacterial infection

Clinically	Well
WBC count	5-15 x 10 ⁹ /L
Bands	<1.5 x 10 ⁹ /L
Urinalysis	10 WBC/HPF
Stool (if diarrhea)	5 WBC/HPF
Past Health	Born >37 wk Home with/before mom No hospitalizations No prior antibiotics use No treated unexplained hyperbilirubinemia No chronic disease

Febrile Infants at Low Risk for Serious Bacterial Infection – An Appraisal of the Rochester Criteria and Implications for Management

Febrile Infant Collaborative Study Group.

Pediatrics 1994; 94(3):390-396

Purpose: To test the hypothesis that infants unlikely to have serious bacterial infection (SBI) can be correctly identified using the Rochester criteria.

Study Characteristics: Prospective study with 1057 infants.

Participants: Febrile infants less than 60 days old.

Intervention: Application of Rochester criteria.

Main Outcomes: Culture of specimens of blood, cerebrospinal fluid and urine for bacteria.

Results: Of the 1057 febrile infants that were involved, 931 were well-looking and 437 met the remaining low risk criteria. The negative predictive value of the low risk criteria was 98.9% (95% CI, 97.2%-99.6%) for SBI.

Conclusions: Low risk Rochester criteria are useful in identifying infants at decreased risk of SBI and antibiotic use may be delayed in these patients.

Infectious Diseases

Table 25. Antibiotic Treatment of Pediatric Bacterial Infections

Infection	Pathogens	Treatment
Meningitis/Sepsis		
Neonatal (birth up to 6 weeks)	GBS, <i>E. coli</i> , <i>Listeria</i> Other: Gram-negative bacilli	Ampicillin + aminoglycoside (gentamicin or tobramycin) (sepsis) Ampicillin + cefotaxime ± vancomycin (meningitis)
6 weeks-3 months	Same pathogens as above and below	Ampicillin + cefotaxime ± cloxacillin if risk of <i>S. aureus</i> (sepsis) Ampicillin + cefotaxime ± vancomycin (meningitis)
>3 mos	<i>S. pneumococcus</i> , <i>N. meningitidis</i> , <i>H. influenzae</i> type b (>5 yrs)	Cefotaxime + vancomycin (sepsis) Ceftriaxone + vancomycin (meningitis)
Otitis Media		
	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>M. catarrhalis</i> , <i>S. pyogenes</i>	1st line: amoxicillin 2nd line: high dose amoxicillin or clavulin 3rd line: high dose clavulin or cefuroxime or ceftriaxone
Strep Pharyngitis		
	Group A beta-hemolytic <i>Streptococcus</i>	Penicillin/amoxicillin or erythromycin (penicillin allergy)
UTI		
	<i>E. coli</i> , <i>Klebsiella</i> , <i>Proteus</i> , <i>Pseudomonas</i> , <i>S. saprophyticus</i> , <i>Enterococcus</i> , GBS	Cephalexin, cefixime (uncomplicated) or IV ampicillin and gentamicin (if complicated) Ampicillin and gentamicin (neonates)
Pneumonia (Community Acquired, Bacterial)		
Neonatal	GBS, Gram-negative bacilli (<i>E. coli</i>), <i>C. trachomatis</i> , <i>S. aureus</i> , <i>Listeria</i>	Ampicillin + gentamicin, add erythromycin if Chlamydia suspected
1-3 mos	<i>S. pneumoniae</i> , <i>C. trachomatis</i> , <i>B. pertussis</i> , <i>S. aureus</i> , <i>H. influenzae</i>	Cefuroxime ± macrolide (erythromycin) or Ampicillin ± macrolide
3 mos-5 yrs	<i>S. pneumoniae</i> , <i>S. aureus</i> , <i>H. influenzae</i> , <i>C. pneumoniae</i> , <i>Mycoplasma pneumoniae</i>	Ampicillin/amoxicillin or clavulin or cefuroxime
>5 years	As above	Macrolide (1st line) or cefuroxime or ampicillin/amoxicillin or clavulin

Fever

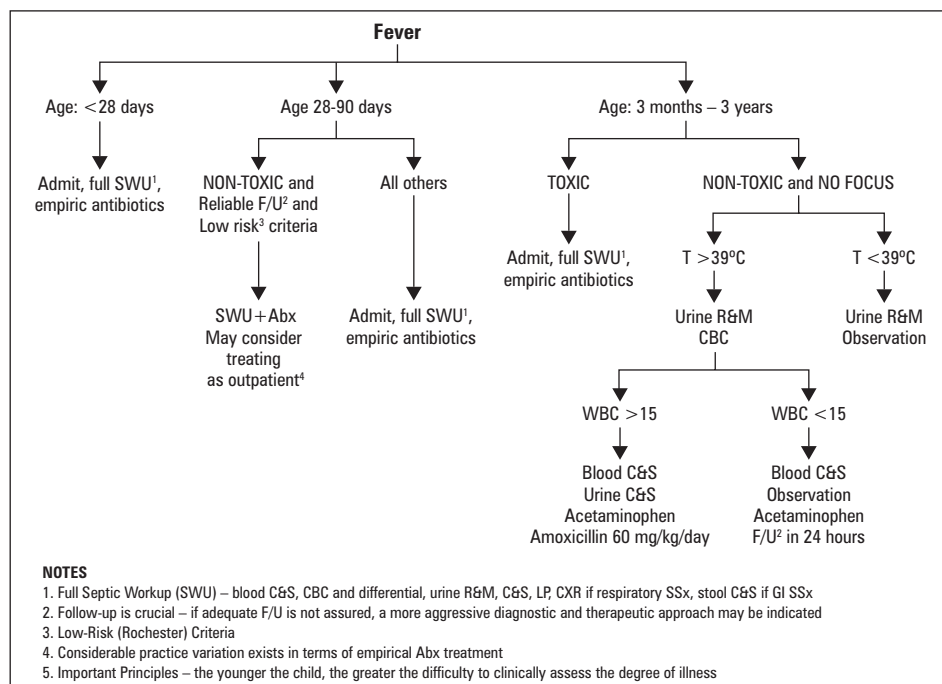


Figure 5. Approach to the Febrile Child

Acute Otitis Media (AOM)

Epidemiology

- peak incidence 3 mo-3 yrs

Etiology

- bacterial (70%) – *S. pneumoniae* (25-40%), non-typable *H. influenzae* (10-30%), *M. catarrhalis* (5-15%), Group A *Streptococcus* (3%), *S. aureus*
- viral (20%) – commonly RSV, influenza, parainfluenza, adenovirus

Definitions

- **certain diagnosis:** 1) recent, usually abrupt, onset of signs and symptoms of middle ear inflammation and effusion 2) presence of middle ear effusion (MEE) 3) middle ear inflammation (MEI)
- **uncertain diagnosis:** does not meet all three criteria
- **severe illness:** moderate to severe otalgia or fever $>39^{\circ}\text{C}$
- **non-severe illness:** mild otalgia and fever $<39^{\circ}\text{C}$

History

- otalgia, tugging at ears, otorrhea, decreased hearing
- irritability, fever, URI symptoms
- nausea, vomiting, diarrhea
- risk factors: bottle feeding, passive smoking, daycare, low SES, cleft lip, Down syndrome, previous/recurrent AOM, family history of recurrent OM, prematurity, male gender, siblings in household
- risk of drug resistance: previous antibiotic therapy in past month, history of AOM, daycare attendance, age 18-24 months, recent hospitalization
- recurrent AOM – 3 episodes in 6 months or 4 episodes in 1 year

Physical Examination

- febrile
- MEE indicated by any of the following on otoscopy: loss of landmarks, bulging tympanic membrane (TM), opaque erythematous TM, yellow fluid behind TM, decreased TM mobility, air-fluid levels behind the TM, otorrhea (if TM perforated)
- MEI indicated by either: distinct erythema of the TM or distinct otalgia (discomfort clearly referable to the ear(s) that results in interference with normal activity or sleep)

Management

- 80% of AOM in children self-resolve without antibiotic therapy, therefore controversy exists surrounding antibiotic use in AOM management
- antibiotics: amoxicillin 80-90 mg/kg/day divided tid
- treatment failure 48-72 hr after initial antibiotic use in severe AOM: ceftriaxone, cefuroxime, or amoxicillin 80-90 mg/kg/day + clavulin 6.4 mg/kg/day
- analgesics: acetaminophen or ibuprofen for pain management
- see Otolaryngology, OT38

Table 26. Treatment of AOM

Age	Certain Diagnosis	Uncertain Diagnosis
<6 mos	Antibacterial therapy x 10d	Antibacterial therapy x 10d
6 mos to 2 yrs	Antibacterial therapy x 10d	Severe illness: antibacterial therapy x 10d Non-severe illness: observation option
≥ 2 yrs	Antibacterial therapy if severe illness x 5d; observation option if nonsevere illness	Observation option

Meningitis

- peak age: 6-12 months; 90% occurs in <5 years old

Risk Factors

- immunocompromised (e.g. HIV, asplenia, prematurity)
- neuroanatomical defects (e.g. dermal sinus, neurosurgery)
- parameningeal infection (e.g. sinusitis, mastoiditis, orbital cellulitis)
- environmental (e.g. daycare centres, household contact)

A Review of Antibiotics for AOM in Children Comparing any Antibiotic Against Observation Indicates that Antibiotic Use has No Significant Impact on Pain at 24 hours and No Significant Effect on Hearing

Cochrane 2004

In older children >6 years, it is appropriate to consider a "wait and see prescription", with instructions for re-evaluation if the child has not improved significantly within 72 hours. In children <2 years with bilateral AOM or AOM with otorrhea, antibiotics are recommended by a recent meta-analysis. (Rovers MM, Glasziou P, Appelman CL, et al, Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet* 2006; 368:1429-1435.)

The Concept and Practice of a Wait-and-See Approach to Acute Otitis Media

Current Opinion in Pediatrics 2008; 20:72-78

Purpose: To summarize recent AOM trials comparing antibiotics versus a "wait and see prescription".

Study Characteristics: Guidelines formulated based on evidence from three recent clinical trials.

Recommendations:

Treat immediately with antibiotics when:

- Age <6 months
- Ill appearance (shock, unresponsive)
- Recurrent AOM
- Suspicion of another concurrent bacterial illness (e.g. pneumonia)
- Recent treatment with antibiotics (within last 7 days)
- Perforated TM (including tympanostomy tubes)
- Immunocompromised
- Craniofacial abnormalities
- Poor access to medical care



Observation option only appropriate if follow-up can be ensured for persistent symptoms. Consider a safety-net antibiotic prescription.

Etiology

- 0-3 months: Group B *Strep.*, *E. coli*, *L. monocytogenes*, other Gram-negatives, viral (HSV, enteroviruses)
- 3 months-3 years: *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, TB, viral (enteroviruses, herpes virus 6, HSV)
- 3-18 years: *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, viral (enteroviruses, adenoviruses, herpes viruses)

Pathophysiology

- URTI → compromise in integrity of mucosa → blood stream invasion from respiratory tract → hematogenous seeding of meninges → meningeal and CNS inflammation

Clinical Presentation

- toxic
- ± URTI prodrome
- fever, lethargy, irritability, photophobia, nausea/vomiting, headache, stiff/sore neck
- younger infants: may not demonstrate localizing signs, may have non-specific symptoms (poor feeding, irritability, lethargy), bulging fontanelle, increasing head circumference
- signs of meningismus
 - Brudzinski's sign: reflex flexion of hips and knees upon active flexion of the neck
 - Kernig's sign: reflex contraction and pain in hamstrings upon extension of leg that is flexed at the hip
 - opisthotonos: spasm in which head and heels are bent backward and body bowed forward
 - nuchal rigidity
- signs of increased ICP: headache, diplopia, ptosis, CN VI palsy, bradycardia with hypertension, apnea, papilledema is uncommon
- seizure in 20-30% of patients with bacterial meningitis
- petechial rash (meningococcemia): associated with poor prognosis



Signs of Meningismus

BONK on the head

Brudzinski's sign

Opisthotonos

Nuchal rigidity

Kernig's sign

Diagnosis

- lumbar puncture (LP) for cerebrospinal fluid (CSF)
 - raised opening pressure (normal: if recumbent and relaxed, less flexed position <160 mm H₂O; if flexed lateral decubitus position = 100-280 mm H₂O)
 - cloudy in bacterial infection
- CSF examination: WBC, protein, glucose, Gram stain, C&S, latex agglutination tests (if partially treated bacterial meningitis), Ziehl-Neelsen stain (if TB suspected)
- viral versus bacterial meningitis
- bloodwork: CBC, blood cultures (positive in 90% cases), blood glucose, electrolytes (to monitor for SIADH)

Table 27. CSF Findings of Meningitis

Component	Normal Child	Normal Newborn	Bacterial Meningitis	Viral Meningitis	Herpes Meningitis
WBC (/μL)	0-6	0-30	>1000	100-500	10-1000
Neutrophils (%)	0	2-3	>50	<40*	<50
Glucose (mg/dL)	40-80	32-121	<30	>30	>30
Protein (mg/dL)	20-30	19-149	>100	50-100	>75
RBC (/μL)	0-2	0-2	0-10	0-2	10-50

*Lymphocytes predominate Modified from Smith A. *Peds in Review* 1993; 14:11-18 and Ahmed A. *et al. Ped Inf Dis J* 1996; 15:298-303

Complications

- mortality: neonate 15-20%, children <1-8%; pneumococcus > meningococcus > Hib
- morbidity: up to 50% may have neurobehavioural morbidity, severe neuro developmental sequelae in 10-20%
- acute
 - SIADH → hyponatremia → brain edema → seizures
 - subdural effusion/empyema
 - brain abscess, disseminated infection (osteomyelitis, septic arthritis, abscess)
 - shock/DIC
- chronic
 - hearing loss
 - intellectual disability, learning disorders
 - neurological deficit, seizure disorder
 - hydrocephalus

Treatment

- isolation with appropriate infection control procedures until 24hr after culture-sensitive antibiotic therapy

- bacterial: empiric antibiotics
- viral: supportive, acyclovir for HSV meningitis
 - most cases of viral meningitis can be sent home (except HSV)
 - if neonatal, use high dose ampicillin as part of regimen until GBS and *Listeria* ruled out
- monitor: glucose, acid-base and volume status
- anticonvulsants may be needed to treat seizures
- prophylaxis
 - *H. influenzae* type b vaccine – routine
 - meningococcal vaccine – if patient has asplenism or complement deficiency, for outbreaks, routine in some provinces
 - pneumococcal vaccine – if immunocompromised or asplenic, routine in some provinces
 - BCG vaccine – if born in TB-endemic area
 - antibiotic prophylaxis for contacts and index case
 - ♦ *H. influenzae* – rifampin
 - ♦ *N. meningitidis* – rifampin, ceftriaxone or ciprofloxacin
- report to public health: acute meningitis (bacterial, viral, other)

Urinary Tract Infection (UTI)

Definition

- urine specimen with $>10^5$ colonies/mL of a single organism

Epidemiology and Etiology

- 3-5% of girls, 1% of boys
 - <1 yr: more common in boys
 - >1 yr F:M = 10:1
- *E. coli* (80-90%), *Klebsiella*, *Proteus* (especially boys), *S. saprophyticus*, *Enterococcus*, and *Pseudomonas*
- risk factors: female, vesicoureteral reflux (VUR), diabetes, immunocompromised, urinary stasis (neurogenic bladder), voiding dysfunction, wiping from back to front

Symptoms and Diagnosis

- cystitis: dysuria, urgency, frequency, suprapubic pain, incontinence, malodorous urine
- pyelonephritis: abdominal or flank pain, fever, malaise, nausea, vomiting (usually as non-specific illness in newborn)
- sterile specimen required: suprapubic aspiration, transurethral catheter, clean catch
- dipstick for nitrates, leukocytes, and blood; urine C&S (definitive diagnosis)
- if systemically ill: CBC, electrolytes, Cr, BUN, blood cultures

Radiologic Evaluation

- U/S to assess for renal growth, hydronephrosis, or structural anomalies and voiding cystourethrography (VCUG) to assess for VUR for all children <2 yrs presenting with febrile UTI
- dimercaptosuccinic acid (DMSA) if VCUG abnormal or history of pyelonephritis to assess for renal scarring
- nuclear studies to follow VUR or assess function

Treatment

- encourage fluid intake (promotes urinary flow)
- uncomplicated UTI: oral cephalexin, or cefixime x 7d
- complicated UTI (acutely ill, $<2-3$ months, vomiting, immunocompromised): admit for hydration, IV ampicillin and aminoglycoside
- prophylaxis: TMP-SMX for higher grades of VUR, awaiting investigations and/or >3 UTIs/yr; Trimethoprim alone if <2 mos
- follow-up
 - if no clinical response within 48 hr re-culture urine

Complications

- long term morbidity: focal renal scarring may lead to hypertension and end-stage renal disease

Pharyngitis and Tonsillitis

Etiology

- viral (adenoviruses, enteroviruses, EBV virus) – 80%
- bacterial (Group A *Streptococcus*) – 20%
- others: fungal (*Candida*), Kawasaki's, retropharyngeal/peritonsillar abscess, epiglottitis, bacterial tracheitis
- cannot be reliably distinguished on clinical features alone



Bagged specimen not useful for ruling in UTI (high false positive rate $>85\%$), but useful for ruling out UTI (high sensitivity).



Sensitivity and Specificity of Urine Dip in Children

	Sensitivity	Specificity
Leukocytes	62%	70%
Nitrites	50%	92%
Both	46%	94%

Walter, et al. The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. *BMC Urol* 2004; 4: 4.

Prophylaxis After First Febrile Urinary Tract Infection in Children? A Multicenter, Randomized Controlled, Noninferiority Trial

Pediatrics 2008; 122:1064-1071

Study: Randomized, controlled, open-label, 2 armed, noninferiority trial.

Patients: 338 patients aged 2 mo to <7 years who had a first episode of febrile UTI.

Intervention: No prophylaxis vs. prophylaxis

Outcome: Recurrence rate of febrile UTI and rate of renal scarring.

Results: No significant difference in recurrence rate or in the rate of renal scarring between the prophylaxis and no prophylaxis group.

Clinical Features

- exudative tonsillitis: GAS, adenovirus, EBV, diphtheria
- soft palate petechiae: GAS, EBV

Table 28. Clinical Features of Pharyngitis

	Viral	Bacterial
Age	<3	>3
Onset	Gradual	Abrupt
Fever	Low-grade	High
Clinical Features	Sore throat Rhinorrhea/cough Conjunctivitis Hoarseness Rash	Sore throat NO rhinitis/ cough Nausea Abdominal discomfort HEENT findings: red pharynx, tender cervical nodes, tonsillar exudates palatal petechiae

Streptococcal (GAS) Pharyngitis

- see Family Medicine, FM47

Clinical Features

- Group A *Streptococcus* (GAS) infection
- most commonly school aged, uncommon in children <3 yrs
- McIsaac Criteria: no cough, tender anterior cervical lymphadenopathy, erythematous tonsils with exudate, fever >38°C, age 3-14
 - score 0-1: no culture, no antibiotics; 2-3: culture, treat if positive; 4: antibiotics

Management

- >2 years old, culture before treatment or do rapid *Strep* antigen test
 - rapid strep test only 70-90% sensitive, therefore culture if negative (throat swab for culture is gold standard, sensitivity 90-95%)
 - pick up 20% of carriers of GAS
- symptomatic
 - if 1 symptom, no culture or antibiotics
 - if >1 symptom, culture then treat with antibiotics
 - ♦ penicillin V or amoxicillin 40 mg/kg/day PO divided bid x 10 days
 - ♦ erythromycin 40 mg/kg/day PO divided tid x 10 days if allergic to penicillin
 - ♦ acetaminophen for discomfort
 - can prevent rheumatic fever if treated within 9-10 days
 - antibiotics do not alter the risk of post-streptococcal glomerulonephritis
 - tonsillectomy for proven, recurrent streptococcal tonsillitis
- complications
 - if untreated, can lead to
 - ♦ suppurative complications: otitis media, sinusitis, cervical adenitis, pneumonia, mastoiditis
 - ♦ direct extension: retropharyngeal/peritonsillar abscess
 - ♦ scarlet fever, rheumatic fever
 - ♦ hematogenous spread: bone/joint infection, meningitis, SBE
 - acute glomerulonephritis (irrespective of antibiotic treatment)
 - invasive GAS disease: illness associated with isolation of GAS from normally sterile sites (blood, CSF, or pleural fluid)
- treatment of invasive GAS disease
 - admit
 - IV clindamycin 40 mg/kg divided into 3-4 doses + IV penicillin 250 000–400 000 U/kg/day divided into 6 doses
- other illnesses caused by strep: impetigo, cellulitis, bacteremia, vaginitis, toxic shock syndrome
- streptococcal toxic shock: illness associated with isolation of GAS from normally sterile sites (blood, CSF, or pleural fluid) + hypotension, renal impairment, coagulopathy, liver impairment, RDS, rash, soft tissue necrosis (necrotizing fasciitis, myositis, or gangrene)

**McIsaac Criteria****Hot LACE****Fever** >38° C

Lymphadenopathy: anterior, tender, cervical

Age 3-14 years

No Cough

Erythematous, exudative tonsils

McIsaac WI, White D, Tannenbaum D, Low DE. *CMAJ* 1998; 158(1):75-83.**Scarlet Fever****4 S and 4 P**

Sore throat

Strawberry tongue

Sandpaper rash

Perioral Sparing

Non-Pruritic

Non-Painful

Peeling

**Scarlet Fever****Appearance:** erythematous, sandpaper rash with strawberry tongue; blanches.**Timing:** 24-48 hours after start of symptoms.**Distribution:** starts in skin folds (i.e. neck, axillae, groin); spreads to trunk with sparing of palms, soles, and perioral area.**SCARLET FEVER**

- erythrogenic strain of Group A *Streptococcus*
- acute onset of fever, sore throat, strawberry tongue
- 24-48 hours after pharyngitis, rash begins in the groin, axillae, neck, antecubital fossa
- within 24 hours, "sandpaper" rash becomes generalized with perioral sparing, non-pruritic, non-painful
- rash fades after 3-4 days, may be followed by peeling
- treatment: penicillin, amoxicillin, or erythromycin (if penicillin allergic) x 10 days

RHEUMATIC FEVER

- inflammatory disease due to antibody cross-reactivity following group A strep infection
- Jones Criteria (revised)
 - requires 2 major OR 1 major and 2 minor PLUS evidence of preceding strep infection (history of scarlet fever, group A streptococcal pharyngitis culture, rapid Ag detection test (only useful if positive), anti-streptolysin O titers (ASOT))
 - major criteria: “SPACE”
 - ♦ Subcutaneous nodules, pea-sized, firm, non-tender nodules typically on extensor surfaces
 - ♦ Pancarditis involving pericardium, myocardium, endocardium
 - ♦ Arthritis (migratory): very tender, red, warm, swollen joints, affects mostly large joints
 - ♦ Chorea (Sydenham's): may be characterized by clumsiness, difficulty with handwriting
 - ♦ Erythema marginatum: begins as pink macules on trunk with central blanching; non-pruritic
 - minor criteria
 - ♦ previous history of rheumatic fever or rheumatic heart disease
 - ♦ polyarthralgia
 - ♦ fever
 - ♦ elevated ESR or C-reactive protein or leukocytosis
 - ♦ prolonged PR interval
- treatment
 - penicillin or erythromycin for acute course x 10 days
 - ASA for arthritis
 - prednisone if severe carditis
- secondary prophylaxis with daily penicillin or erythromycin; course depends on:
 - without carditis: 5 years or until 21 years old, whichever is longer
 - with carditis but no residual heart disease (no valvular disease): 10 years or longer
 - carditis and residual heart disease (persistent valvular disease): at least 10 years since last episode, sometimes life long prophylaxis
- complications
 - acute: myocarditis, conduction system (sinus tachycardia, atrial fibrillation), valvulitis (acute MR), pericarditis
 - chronic: rheumatic valvular heart disease (mitral and/or aortic insufficiency/stenosis), increased risk of infectious endocarditis ± thromboembolic phenomenon
 - onset of symptoms usually after 10-20 year latency from acute carditis of rheumatic fever

Infectious Mononucleosis

- the “great imitator”: systemic viral infection that affects many organ systems
- Epstein-Barr virus (EBV): a member of herpesviridae
- incubation: 1-2 months
- spread through saliva (“kissing disease”), sexual activity

Clinical Features

- prodrome: 2-3 days of malaise, anorexia
- infants and young children: often asymptomatic or mild disease
- older children and young adults: may develop typical infectious mononucleosis syndrome
 - fever, tonsillar exudate, generalized lymphadenopathy, pharyngitis
 - ± hepatosplenomegaly
 - ± rash (rash more frequent with patients treated with amoxicillin/ampicillin)
 - any “-itis” (including arthritis, hepatitis, nephritis, myocarditis)
 - chronic fatigue
- resolves over 2-3 weeks although fatigue may persist for several months
- administration of amoxicillin results in rash in >90% of cases

Complications

- aseptic meningitis, encephalitis, Guillain-Barré, splenic rupture, agranulocytosis, myocarditis (rare)

Diagnosis

- heterophil antibody test (Monospot® test) is 85% sensitive in adults and older children, but only 50% sensitive <4 yrs of age
- false positive results with HIV, SLE, lymphoma, rubella, parvovirus
- EBV titres
- CBC and differential: atypical lymphocytes, lymphocytosis, Downey cells, ± anemia, ± thrombocytopenia

Treatment

- throat culture to rule out streptococcal pharyngitis
- supportive care (bed rest, fluids, saline gargles for sore throat, acetaminophen)
- if airway obstructed secondary to node and/or tonsillar enlargement, admit to hospital for steroids
- splenic enlargement often not apparent clinically so all patients should avoid contact sports for 6-8 weeks
- acyclovir not useful

Pertussis

- *Bordetella pertussis*, whooping cough, “100-day cough”
- incubation: 6-20 days; infectivity: 1 week before paroxysms to 3 weeks after
- increase in number of reported cases since early 1990's
- spread: highly contagious via air droplets released during intense coughing
- greatest incidence among children <1 year and adolescents

Clinical Presentation

- prodromal catarrhal stage
 - 1-2 weeks, most contagious
 - coryza, mild cough
- paroxysmal stage
 - 2-4 weeks
 - paroxysms of cough, sometimes followed by inspiratory whoop (whoop may be absent in children <6 months or adults)
 - infants may present with apnea
 - ± vomiting with coughing spells
 - onset of attacks precipitated by yawning, sneezing, eating, physical exertion
 - can have severe symptoms for 6 weeks, cough for 6 months
 - pressure effect – subconjunctival hemorrhage, rectal prolapse, hernias, epistaxis
- convalescent stage
 - 1-2 weeks, noninfectious
 - occasional paroxysms of cough, but decreased frequency and severity, lasts up to 6 months

Diagnosis

- clinical: URTI symptoms followed by paroxysms of cough in an afebrile child
- lymphocytosis
- PCR of nasopharyngeal swab or aspirate

Complications

- otitis media
- respiratory complications
 - sinusitis, secondary pneumonia, atelectasis, pneumomediastinum, pneumothorax, interstitial or subcutaneous emphysema secondary to ruptured alveoli
- neurological complications
 - seizures, encephalopathy (1:100,000), intracranial hemorrhage

Treatment

- supportive care
- hospitalize if paroxysms of cough are associated with cyanosis and/or apnea and give O₂
- erythromycin 40 mg/kg/day x 10 days started within 3 weeks after onset of cough
 - isolate until 5 days of treatment
 - treatment will decrease infectivity but not change course of illness
 - shortens period of communicability
- antibiotic prophylaxis: macrolides for all household contacts
- prevention: acellular pertussis vaccine (Pentacel®) in infants and children, and pertussis booster (Adacel®) in adolescents and adults

Varicella (Chickenpox)

- varicella-zoster virus (VZV)
- incubation: 10-21 days, infectivity: 1-2 days pre-rash until vesicles have crusted over
- transmission rate is 86% in household contacts; spreads via respiratory secretions (airborne) and vesicular fluid
- primary infection with virus usually results in life-long immunity: >95% of young adults with varicella are immune
- maternal infection in first or early second trimester (<2% risk) can cause congenital varicella syndrome (low birth weight, CNS abnormalities, digit/limb abnormalities, cutaneous scarring, eye defects)
- maternal infection 5 days before to 2 days after delivery can lead to severe varicella of neonate

Clinical Presentation

- 1-3 day prodrome: fever and respiratory symptoms
- characteristic polymorphous rash
 - very pruritic
 - crops of red macules, which quickly become vesicles surrounded by erythema
 - “dewdrop on erythematous base”
 - vesicles burst and lesions crust over
 - on trunk, face, scalp, conjunctivae, vagina, oral mucosa, palms and soles
 - new crops usually stop forming after 5-7 days



Varicella

Appearance: macules → papules → vesicles → crusting; all stages apparent at once.

Timing: 10-21 day incubation; rash 1-3 days after start of symptoms.

Distribution: face, trunk, extremities, mucosa, palms and soles.

Complications

- **secondary bacterial infection** (most common)
 - infection with staph, GAS
 - presents as impetigo, abscesses, cellulitis, necrotizing fasciitis, sepsis
- cerebellar ataxia, pneumonia, hepatitis, encephalitis
- immunocompromised patients: varicella may be life-threatening
- neonates born to mothers who develop varicella from 5 days before to 2 days after delivery are considered high risk
 - must administer varicella-zoster immune globulin (VZIG), follow for signs of infection/sepsis, and consider starting acyclovir
- virus latent in sensory ganglia and reappears as herpes zoster in 68/100,000 individuals
 - incidence is increased in immunocompromised patients

Treatment

- supportive (hydration, acetaminophen, antipruritics, AVOID salicylates)
- proper hygiene, discourage scratching
- acyclovir for severe disease, immunocompromised patients, neonates
- avoid contact with others until lesions are dry and crusted and no new ones are appearing

Prophylaxis and Prevention

- immunization important to prevent complications (see *Routine Immunization*, P4)
- VZIG for post-exposure in high risk susceptible patient (within 96 hours of exposure)

**Complications of VZV****SHAPE**

Secondary bacterial infection
Hepatitis
Cerebellar Ataxia
Pneumonia
Encephalitis

**Absolute Contraindication**

Do not use ASA in children due to the risk of Reye syndrome with varicella and influenza.

Roseola

- human herpes virus 6
- incubation: 5-15 days; infectivity and spread: unknown
- typically affects children <3 years

Clinical Presentation

- high fever (>39.5°C) lasting 3-5 days, cough, respiratory symptoms, nasal congestion
- pharynx, tonsils and tympanic membranes are erythematous
- cervical, posterior cervical lymphadenopathy, bulging anterior fontanelle (if CNS involvement)
- fever ceases before rash appears
 - pink non-pruritic macules and maculopapules
 - macules coalesce and disappear in 1-2 days

Treatment

- supportive (acetaminophen)

Complications

- febrile seizures
- encephalitis

**Roseola**

Appearance: pink maculopapular rash (faint).

Timing: 5-15 day incubation; rash 3-5 days after symptoms.

Distribution: starts at neck and trunk spreading to face and extremities.

Measles

- morbillivirus
- incubation: 10-14 days; infectivity: 4 days pre-rash, spread by airborne route

Clinical Presentation

- prodrome: “3 C’s” – cough, coryza, conjunctivitis, fever, eyelid edema
- Koplik spots (1-2 days before and after rash): small white papules on red base on buccal mucosa
- maculopapular rash spreads from face and hairline spreading in a descending fashion on the body over 3 days

Diagnosis

- clinical examination and positive serology for measles IgM

Treatment

- supportive and symptomatic (appropriate treatment of secondary bacterial infection)
- prophylactic immunoglobulin to prevent disease if administered within 6 days of exposure
- vitamin A supplementation in selected children

Complications

- secondary bacterial infection (laryngotracheobronchitis, otitis media, sinusitis), bronchopneumonia, croup
- encephalitis (1:1000): ataxia, vomiting, seizures, coma
- subacute sclerosing panencephalitis (1:100,000): slow measles virus infection of brain manifesting years later, characterized by progressive cerebral deterioration with myoclonic jerks, fatal within 6-12 months

**Measles**

Appearance: erythematous, maculopapular rash; Koplik spots.

Timing: 10-14 day incubation; rash 3 days after start of symptoms.

Distribution: starts at hairline spreading downwards; palms and soles typically not involved.

Mumps

- paramyxovirus
- incubation: 12-25 days; infectivity: 7 days pre-parotitis to 7 days post-parotitis, spread by droplets
- diagnosis: urine or saliva for viral serology

Clinical Presentation

- fever, headache, parotitis (bilateral; pushes earlobes up and out), myalgia, malaise
- 30-40% of cases are subclinical with minimal symptoms

Treatment

- supportive

Complications

- meningoencephalomyelitis: over 10% of patients with parotitis
- orchitis, epididymitis, infertility
- pancreatitis: may see elevated serum amylase without symptoms
- other: ocular complications, thyroiditis, hearing impairment, myocarditis, arthritis, thrombocytopenia, cerebellar ataxia, glomerulonephritis

Rubella

- rubivirus
- incubation: 14-21 days
- infectivity: 7 days pre-rash to 5 days post-rash, spread by droplets
- diagnosis: serology for rubella IgM; may not be detected 4-5 days after rash onset

Clinical Presentation

- prodrome of nonspecific respiratory symptoms and suboccipital adenopathy
- rash
 - pink, maculopapular, initially on face, then spreading to entire body
 - pruritic, disappearing by fourth day
- congenital rubella syndrome (CRS)
 - mother infected in first 4 months of pregnancy (highest risk)
 - infection in utero, failure of rubella vaccine is <5% and rarely results in CRS
 - cataracts/congenital glaucoma, congenital heart disease, hearing impairment (common), purpura ("blueberry muffin baby"), hepatosplenomegaly, jaundice, microcephaly, developmental delay, radiolucent bone disease
 - prevention: routine childhood immunization, ensure immunity of women of childbearing age with vaccination

Treatment

- symptomatic

Prognosis

- excellent prognosis in patients with acquired disease
- irreversible defects in congenitally infected patients

Complications

- arthritis/arthralgia: polyarticular (fingers, wrists, knees), lasts days to weeks
- encephalitis

Erythema Infectiosum

- parvovirus B19, "fifth disease"
- incubation: 4-14 days; infectivity: prior to onset of rash

Clinical Presentation

- initial 7-10 days: flu-like illness with fever
- day 10-17: rash appears (immune response)
 - raised, uniform maculopapular lesions on cheeks ("slapped cheek" appearance), forehead, chin, circumoral sparing
 - warm, nontender, may be pruritic, may also appear on extensor surfaces, trunk, neck, buttocks
- days to weeks: rash fades, may reappear with local irritation (heat, sunlight)

Treatment

- supportive
- blood transfusions for some with aplastic crisis



Rubella

Appearance: pink, maculopapular rash.

Timing: 14-21 day incubation; rash

1-5 days after start of symptoms.

Distribution: starts on face spreading to neck and trunk.



Erythema Infectiosum

Appearance: uniform, erythematous, maculopapular rash.

Timing: 4-14 day incubation; rash 10-17 days after symptoms.

Distribution: bilateral cheeks with circumoral sparing; can affect trunk and extremities.

Complications

- arthritis (10%, pain and stiffness in peripheral joints), vasculitis
- infection during pregnancy may lead to fetal hydrops, fetal loss
- aplastic crisis: reticulocytopenia occurs for 1 week during illness, unnoticed in normal individuals, but severe anemia in patients with chronic hemolytic anemia

Reye Syndrome

- acute hepatic encephalopathy and noninflammatory fatty infiltration of liver and kidney
- mitochondrial injury of unknown etiology results in reduction of hepatic mitochondrial enzymes, diagnosis by liver biopsy
- associated with aspirin ingestion by children with varicella or influenza infection
- 40% mortality

Clinical Presentation

- vomiting
- hyperventilation, tachycardia, decerebrate posturing
- respiratory failure
- agitated delirium, coma, death

Treatment

- should be tailored based on severity of presentation
- IV glucose (to counteract effects of glycogen depletion)
- fluid restriction, mannitol (if cerebral edema)
- prevention: avoid aspirin with viral illness

HIV Infection

- see [Infectious Diseases](#), ID29

Epidemiology

- risk of vertical transmission in 20-30% born to untreated HIV infected women (risk decreases to <1% with appropriate antiretroviral treatment during pregnancy)
- transmission
 - infants and children: transplacental (most common), maternal blood, breast milk
 - adolescents: sexual intercourse, needles (IV drug use and tattoos), blood products

Risk Factors

- HIV positive mother
- IV illicit drug use (IVDU)
- mother is with HIV positive partner
- unprotected sex
- sexual abuse
- receipt of blood products (rare)

Incubation

- time from contracting infection to developing symptoms is usually <2 years, but can be several years

Clinical Features of AIDS in Infants and Children

- signs and symptoms occur often within the first year, most within two years of age
 - encephalopathy
 - recurrent/persistent thrush
 - chronic interstitial pneumonitis (relatively common); *Pneumocystis jiroveci pneumonia* (PJP) infection (formerly PCP)
 - hepatomegaly
 - failure to thrive, opportunistic infections, lymphadenopathy

HIV Testing

- 1st step: screening for HIV Ab with ELISA
- if positive do 2nd step: confirmatory test for Ab using Western blot or immunofluorescence (sensitivity and specificity of 99%)
 - maternal HIV antibodies can persist up to 18 months (can result in a false positive HIV test), typically retest every 6 months from 0-18 months if asymptomatic
 - if breastfeeding, repeat test 3 months after stopping breastfeeding
- other tests: viral nucleic acid by PCR, viral culture, viral antigen
- if sexually active, must re-test 6 months after 1st test (if negative)

Management

- adequate nutrition (breastfeeding contraindicated in developed countries)
- prompt treatment of infections
- prophylaxis
 - TMP/SMX for PJP
 - azithromycin for mycobacterium avium complex (MAC)
 - nystatin, ketoconazole, acyclovir if indicated
- \pm IVIG
- immunizations
 - all routine immunizations (including MMR and varicella if well)
 - pneumococcal and influenza vaccines
 - avoid OPV, BCG, and yellow fever
- suppression of HIV
 - HAART (highly active antiretroviral therapy)
- HIV positive pregnant women should be offered antiretroviral therapy along with resources for formula feeding to decrease perinatal transmission
 - elective C-section if not on therapy or if significant viral load

Neonatology

Normal Baby at Term

- RR: 40-60 breaths/min
- HR: 90-170 beats/min
- sBP: 70-90 mmHg; dBP: 30-40 mmHg
- weight: 2,500-4,500 g
- glucose: >2.6 mmol/L (45 mg/dL)

Gestational Age (GA) and Size

Definitions

- classification by gestational age (GA)
 - pre-term: <37 weeks
 - term: 37-42 weeks
 - post-term: >42 weeks
- classification by birth weight
 - small for gestational age (SGA): 2 SD $<$ mean weight for GA or $<3^{\text{rd}}$ percentile
 - appropriate for gestational age (AGA): within 2 SD of mean weight for GA
 - large for gestational age (LGA): 2 SD $>$ mean weight for GA or $>97^{\text{th}}$ percentile

Table 29. Abnormalities of Gestational Age and Size

Features	Causes	Problems
Pre-term Infants <37 weeks	Most common cause unknown Maternal disease e.g. pre-eclampsia Drugs/EtOH, smoking Chromosomal Multiple pregnancy Placental insufficiency	Respiratory distress syndrome, apnea of prematurity, chronic lung disease, bronchopulmonary dysplasia Feeding difficulties, necrotizing enterocolitis (NEC) Hypocalcemia, hypoglycemia, hypothermia Anemia, jaundice Retinopathy of prematurity Intracranial/intraventricular hemorrhage Patent ductus arteriosus (PDA)
Post-term Infants >42 weeks Wizened-looking, leathery skin Meconium staining	Hypoglycemia	Hypoxia, meconium aspiration
SGA Infants $<3^{\text{rd}}$ percentile Asymmetric (head-sparing): late onset, growth arrest	Extrinsic causes: placental insufficiency, poor nutrition, hypertension, multiple pregnancies, drugs, EtOH, smoking	Perinatal hypoxia Hypoglycemia, hypocalcemia, hypothermia Hyperviscosity (polycythemia), jaundice Hypomotility
Symmetric: early onset, lower growth	Intrinsic causes: maternal infections (TORCH), congenital abnormalities, syndromal, idiopathic	Patent ductus arteriosus (PDA)
LGA Infants $>97^{\text{th}}$ percentile	Maternal diabetes Racial or familial factors Certain syndromes	Birth trauma, perinatal hypoxia, meconium aspiration, respiratory distress syndrome, transient tachypnea of newborn (TTN), persistent pulmonary hypertension (PPHN) Jaundice, polycythemia Hypoglycemia, hypocalcemia

**Dubowitz/Ballard Scores**

GA can be determined after birth using Dubowitz/Ballard scores:

- Assessment at delivery of physical maturity (e.g. plantar creases, lanugo, ear maturation) and neuromuscular-maturity (e.g. posture, arm recoil) translates into a score from -10 to +50
- Higher score means greater maturity (increased GA)
- -10 = 20 weeks; +50 = 44 weeks
- Ideal = 35-40 which corresponds to GA 38-40 weeks
- Only accurate ± 2 weeks

Routine Neonatal Care



- performed in delivery suite
- 1. erythromycin ointment – applied to both eyes for prophylaxis of gonococcal ophthalmia neonatorum
- 2. vitamin K IM – to avoid hemorrhagic disease of newborn
- 3. screening tests
 - varies across Canada and United States
 - new tandem mass spectrometry (MS/MS) can detect 25 inborn errors of metabolism (IEM) in a single process from heel prick
 - ♦ 100% sensitivity and 83-99% specificity depending on IEM
 - in Ontario, newborn screening tests for
 - ♦ endocrine disorders (congenital adrenal hyperplasia, congenital hypothyroidism)
 - ♦ cystic fibrosis
 - ♦ hemoglobinopathies (HbSS, HbSc, sBthal)
 - ♦ inborn errors of metabolism (22 in total)
 - 3 categories: fatty acid oxidation defects, aminoacidopathies, organic acid defects
 - others: biotinidase deficiency and galactosemia
- 4. if mother Rh negative: send cord blood for blood group and direct antiglobulin test
- 5. if indicated: G6PD deficiency testing
- 6. if mother hepatitis B surface antigen positive: HBIG and start hepatitis B vaccine series

Approach to the Depressed Newborn



- a depressed newborn lacks one or more of the following characteristics for a normal newborn
 - pulse >100 bpm
 - cries when stimulated
 - actively moves all extremities
 - has a good strong cry
- between 5-10% of newborn babies require assistance with breathing after delivery

Table 30. Etiology of Respiratory Depression in the Newborn

Etiology	Examples
Respiratory Problems	Respiratory distress syndrome/Hyaline membrane disease CNS depression Meconium aspiration Pneumonia Pneumothorax
Anemia (severe)	Erythroblastosis fetalis Secondary hydrops fetalis
Maternal Causes	Drugs/anesthesia Diabetes mellitus Pregnancy-induced hypertension
Congenital Malformations/Birth Injury	Nuchal cord
Shock/Cyanosis/Congenital Heart Disease	
Other	Hypothermia Hypoglycemia Infection

Diagnosis

- vital signs
- detailed maternal history
 - include prenatal care, illnesses, use of drugs, labour, previous high risk pregnancies, infections during pregnancy, current infections, duration of ruptured membranes, blood type and Rh status, amniotic fluid status, gestational age, meconium, Apgar scores
- clinical findings (observe for signs of respiratory distress: cyanosis, tachypnea, retractions, and grunting)
- laboratory results (CBC, ABG, pH, blood type)
- transillumination or chest x-ray (if suspecting pneumothorax or diaphragmatic hernia)

Management

- ABC's
- suction if meconium present and infant is depressed
- apply tactile stimulation
- provide air/oxygen and assisted ventilation if apneic or HR <100 bpm
- monitor oxygen saturation and heart rate (if HR <60 bpm, start chest compressions)
- treat the underlying cause
- counsel and provide explanation and support to family

Neonatal Resuscitation

- assess Apgars at 1 and 5 minutes
- if <7 at 5 minutes then reassess q5 min, until >7
- do not wait to assign Apgar score before initiating resuscitation



Apgar Score

Appearance (colour)
Pulse (heart rate)
Grimace (irritability)
Activity (tone)
Respiration (respiratory effort)

Or: "How Ready Is This Child?"
See Table 31

Table 31. Apgar Score

Sign	0	1	2
Heart Rate	Absent	<100/min	>100/min
Respiratory Effort	Absent	Slow, irregular	Good, crying
Irritability	No response	Grimace	Cough/cry
Tone	Limp	Some flexion of extremities	Active motion
Colour	Blue, pale	Body pink, extremities blue (acrocyanosis)	Completely pink

Initial Resuscitation

- anticipation – know maternal history, history of pregnancy, labour, and delivery; prepare equipment
- steps to take for all infants (before ABC's)
 - provide warmth: warm (radiant heater, warm towels), dry the newborn (remove wet towels)
 - position and clear airway: "sniffing" position
 - stimulate infant (if needed): rub back gently or flick soles of feet EXCEPT if meconium present (in which case suction FIRST)
 - assess breathing, heart rate and colour
- **Airway**
 - if meconium is present and
 - ♦ baby is vigorous (strong respiratory effort, good muscle tone, HR >100): suction mouth and nose after delivery of head
 - ♦ baby is not vigorous: free flow O₂, intubate and suction trachea
 - if no meconium is present, remove secretions by wiping mouth and nose with towel or gentle suction of mouth then nose
- **Breathing**
 - if HR <100 or apneic, apply positive pressure ventilation (PPV)
 - PPV at rate of 40-60/min, with enough pressure to see visible chest expansion
- **Circulation**
 - if HR <60 after 30 sec of effective ventilation, start chest compressions ("60 or less, compress")
 - chest compressions at lower 1/3 of the sternum at 1/3 of the AP depth at a rate of 120 events per min (3 compressions:1 ventilation = 90 compressions/min:30 breaths/min)

Table 32. Interventions Used in Neonatal Resuscitation

Intervention	Schedule	Indications	Comments
epinephrine (adrenalin)	0.1-0.3 mL/kg/dose of 1:10 000 solution IV 0.3 – 1.0 mL intratracheal q3-5 min prn	HR <60 and not rising	Side effects: tachycardia, hypertension, cardiac arrhythmias
naloxone (Narcan®)	0.1 mg/kg of a 0.4 mg/mL solution (= 0.25 mL/kg/dose) IV/IM/SC	Newborn with respiratory depression and maternal narcotic use 4 hours before delivery	Do not use for chronic opiate exposure – may cause withdrawal symptoms including hypertension, irritability, poor feeding Action of narcotic outlasts action of naloxone
fluid bolus (NS, whole blood, Ringer's lactate)	10 mL/kg/dose over 5-10 min	Evidence of hypovolemia	



Chronic Perinatal Infections

CHEAP TORCHES

Chicken pox / shingles
Hepatitis B
Ebstein-Barr virus
AIDS (HIV)
Parvovirus B19 (erythema infectiosum)
Toxoplasmosis
Other
Rubella virus
Cytomegalovirus/Coxsackievirus
Herpes simplex virus
Every STI
Syphilis

• See *Obstetrics*, OB19

Sepsis in the Neonate

Table 33. Sepsis Considerations in the Neonate

Early Onset (0-5 days)	Late Onset (5-28 days)
Vertical transmission, 95% present within 24 hr	Acquired after birth
Risk factors:	Most common in preterm infants in NICU (due to coagulase negative staph)
Maternal infection: UTI, GBS positive, previous child with GBS sepsis or meningitis	Also in healthy, full-term
Maternal fever/leukocytosis/chorioamnionitis	Same pathogens plus:
Prolonged rupture of membranes (>18 hrs)	<i>Streptococcus</i> , <i>Staphylococcus</i>
Preterm labour	
Pathogens: GBS, <i>E. coli</i> , <i>Listeria</i>	

Signs of Sepsis

- no reliable absolute indicator of occult bacteremia in infants <3 months, most specific result has been WBC <5
- temperature instability (hypo/hyperthermia)
- respiratory distress, cyanosis, apnea
- tachycardia/bradycardia
- lethargy, irritability
- poor feeding, vomiting, abdominal distention, diarrhea
- hypotonia, seizures, confusion, lethargy, coma
- jaundice, hepatomegaly, petechiae, purpura

Cyanosis**Approach to Neonatal Cyanosis**

- 2 major types
- **peripheral cyanosis**
 - can be normal transiently but may indicate sepsis or temperature instability
- **central cyanosis**
 - deoxygenated hemoglobin
 - ♦ respiratory
 - upper (choanal atresia, macroglossia, airway hypoplasia, laryngeal web/cyst, foreign body)
 - lower (pneumonia, meconium aspiration syndrome (MAS), pneumothorax, diaphragmatic hernia, AV fistula, pulmonary hypoplasia)
 - ♦ cardiovascular (congenital heart disease, PPHN)
 - ♦ neurologic
 - CNS (asphyxia, hemorrhage, seizure, narcotics/sedatives)
 - neuromuscular (myasthenia gravis, botulism)
 - ♦ hematologic (polycythemia)
 - ♦ sepsis
 - abnormal hemoglobin (methemoglobinemia, carboxyhemoglobinemia)



Carboxyhemoglobinemia (secondary to carbon monoxide poisoning) results in impaired binding of oxygen to hemoglobin but does not discolour the blood. Therefore it may not register on pulse-oximetry and cyanosis may not be evident clinically.

Methemoglobinemia pulse oximetry typically reads higher than the true level of oxyhemoglobin. This is due to the fact that methemoglobin alters the absorption of red light at the two wavelengths that pulse oximetry uses to predict oxygen saturation.

Management

- ABGs
 - elevated CO₂ suggests respiratory cause
 - hyperoxic test (to rule out CHD): get baseline pO₂ in room air, then pO₂ on 100% O₂ for 10-15 min
 - pO₂ <150 mmHg: suggests congenital heart disease (see *Pediatric Cardiology*, P22)
 - pO₂ >150 mmHg: suggests respiratory (airway, chest, lungs), brain or blood problems
- CXR – look for respiratory abnormalities (respiratory tract malformations, evidence of shunting, pulmonary infiltrates) and cardiac abnormalities (cardiomegaly, abnormalities of the great vessels)

Persistent Pulmonary Hypertension of the Newborn (PPHN)**Clinical Presentation**

- incidence 1.9/1000 live births
- present within 12 hours of birth with severe hypoxemia/cyanosis but relatively mild respiratory distress

Pathophysiology

- persistence of fetal circulation as a result of persistent elevation of pulmonary vascular resistance
- R → L shunt through PDA, foramen ovale, intrapulmonary channels → decreased pulmonary blood flow and hypoxemia → further pulmonary vasoconstriction

Risk Factors

- asphyxia, MAS, RDS, sepsis, structural abnormalities (e.g. diaphragmatic hernia, pulmonary hypoplasia) (secondary PPHN)
- primary PPHN occurs in absence of risk factors

Investigations

- measure pre- and post-ductal oxygen levels
- echocardiogram reveals increased pulmonary artery pressure and a R → L shunt, also used to rule out other cardiac defects

Treatment

- maintain good oxygenation ($\text{SaO}_2 > 95\%$) in at-risk infants
- O_2 given early and tapered slowly, minimize stress and hypoxia, alkalization, inotropes (to make systemic pressure greater than pulmonary pressure)
- mechanical ventilation, high frequency oscillation (HFO)
- nitric oxide
- extracorporeal membrane oxygenation (ECMO) used in some centres

Apnea

- “periodic breathing” is a normal respiratory pattern seen in newborns in which periods of rapid respiration are alternated with apneic episodes lasting 5-10 seconds
- apnea: absence of respiratory gas flow for more than 15-20 seconds (or less if associated with bradycardia or cyanosis) – 3 types
 - central: no chest wall movement
 - obstructive: chest wall movement continues
 - mixed: combination of central and obstructive apnea

Differential Diagnosis

- in term infants, apnea always requires full work-up
- apnea <24 hrs – strongly associated with sepsis
- apnea >24 hrs
 - CNS
 - ♦ apnea of prematurity: combination of CNS prematurity and obstructive apnea, resolves by 36 weeks GA, diagnosis of exclusion
 - ♦ seizures
 - ♦ intracranial hemorrhage (ICH)
 - ♦ hypoxic injury
 - infectious: sepsis, meningitis, necrotizing enterocolitis (NEC)
 - GI: gastroesophageal reflux disease (GERD), aspiration with feeding
 - metabolic: hypoglycemia, hyponatremia, hypocalcemia
 - cardiovascular: low and high blood pressure, anemia, hypovolemia, PDA, heart failure
 - drugs: morphine

Management

- O_2 , continuous positive airway pressure (CPAP), mechanical ventilation
- tactile stimulation
- correct underlying cause
- medications – methylxanthines (caffeine) stimulate the CNS and diaphragm and are used for apnea of prematurity (not in term infants)

Respiratory Distress in the Newborn**Clinical Presentation**

- tachypnea: RR >60/min; tachycardia: HR >160/min
- grunting, intercostal indrawing, nasal flaring
- dusky skin, central cyanosis
- decreased air entry, crackles on auscultation

Differential Diagnosis of Respiratory Distress

- pulmonary
 - respiratory distress syndrome (RDS)
 - transient tachypnea of the newborn (TTN)
 - meconium aspiration syndrome (MAS)
 - pleural effusions, pneumothorax
 - congenital lung malformations
- infectious
 - sepsis
 - pneumonia (GBS + others)
- cardiac
 - congenital heart disease (cyanotic, acyanotic)
 - persistent pulmonary hypertension of the newborn (PPHN)
- hematologic
 - blood loss
 - polycythemia

- anatomic
 - tracheoesophageal fistula
 - congenital diaphragmatic hernia
 - upper airway obstruction (see Otolaryngology, OT43)
 - ♦ choanal atresia
 - ♦ Pierre-Robin sequence (retrognathia and/or micrognathia plus cleft palate, and glossoptosis)
 - ♦ laryngeal (malacia)
 - ♦ tracheal (malacia, vascular ring)
 - ♦ mucous plug
 - ♦ cleft palate
- metabolic
 - hypoglycemia
 - inborn errors of metabolism (amino acidemia, organic acidemia, urea cycle disturbance, galactosemia, 1° lactic acidosis)
- neurologic
 - CNS damage (trauma, hemorrhage)
 - drug withdrawal syndromes

Investigations

- CXR, ABG or capillary blood gas
- CBC, blood cultures, blood glucose
- ECHO, ECG if indicated

Respiratory Distress Syndrome (RDS)

- also known as “hyaline membrane disease”

Pathophysiology

- surfactant deficiency → poor lung compliance due to high alveolar surface tension → atelectasis → decreased surface area for gas exchange → hypoxia + acidosis → respiratory distress
- surfactant decreases alveolar surface tension, improves lung compliance and maintains functional residual capacity
- there is usually sufficient surfactant production by 36 weeks



RDS is the most common cause of respiratory distress in the preterm infant.

Risk Factors

- prematurity
- low birth weight
- maternal diabetes: insulin inhibits the cortisol surge necessary for surfactant synthesis
- C-section without labour
- asphyxia, meconium aspiration
- acidosis, sepsis
- males > females
- hypothermia
- second born twin

Clinical Presentation

- signs of respiratory distress (tachypnea, tachycardia, grunting, intercostal indrawing, nasal flaring, cyanosis, lung crackles)
- onset within first few hours of life, worsens over next 24-72 hours
- infants may develop respiratory failure and require ventilation
- CXR: decreased aeration and lung volumes, reticulonodular pattern throughout lung fields with air bronchograms, atelectasis; may resemble pneumonia, if severe can see white-out

Prevention

- steroid therapy (e.g. Celestone® 12 mg q24h x 2 doses) for mothers who are at risk of preterm birth
- monitor lecithin:sphingomyelin (L/S) ratio with amniocentesis, L/S >2:1 indicates lung maturity
- prophylactic surfactant often given to high risk infants (<28 weeks) at birth



“Ground glass” appearance of lungs is pathognomonic of RDS.

Treatment

- supportive
 - O₂, assisted ventilation (CPAP, or intubation and mechanical ventilation)
 - administer fluids cautiously to avoid pulmonary edema
- endotracheal surfactant administration

Prognosis

- in severe prematurity and/or prolonged ventilation, increased risk of bronchopulmonary dysplasia (BPD)/chronic lung disease

Complications

- bronchopulmonary dysplasia
- pulmonary air leaks (pneumothorax)

Transient Tachypnea of the Newborn (TTN)

- also known as “wet lung syndrome” and respiratory distress syndrome type II

Pathophysiology

- delayed resorption of fetal lung fluid → accumulation of fluid in peribronchial lymphatics and vascular spaces → tachypnea

Risk Factors

- full term or near-term infant
- no labour/short labour (hypothesized lack of catecholamine release)
- C-section (lungs are not compressed during passage through pelvic floor)
- diabetic mother/gestational weight >4500 g
- maternal asthma
- male sex

Clinical Presentation

- tachypnea within the first few hours of life, mild retractions, grunting, nasal flaring, without signs of severe respiratory distress
- usually resolves in 24-72 hours
- CXR: fluid in fissures, increased vascularity, slight cardiomegaly

Treatment

- supportive: O₂, careful fluid administration, may use CPAP

Prognosis

- full recovery expected within 2-5 days
- children with TTN may be at increased risk of developing wheezing syndromes (such as asthma) in childhood

Meconium Aspiration Syndrome (MAS)

- 10-15% of all infants are meconium stained at birth, ~5% of meconium stained infants get MAS
- usually associated with fetal distress in utero or post-term infants
- meconium is sterile but causes airway obstruction, chemical inflammation, and surfactant inactivation

Clinical Presentation

- respiratory distress within hours of birth
- small airway obstruction, chemical pneumonitis → tachypnea, barrel chest with audible crackles
- CXR: hyperinflation, streaky atelectasis, patchy and coarse infiltrates
- 10-20% have pneumothorax

Complications

- hypoxemia, hypercapnea, acidosis, PPHN, pneumothorax, pneumomediastinum, pneumonia, sepsis, respiratory failure, death

Treatment

- supportive care, assisted ventilation (important to maintain adequate oxygenation)
- ventilated infants often require sedation
- may benefit from surfactant replacement
- inhaled nitric oxide, extracorporeal membrane oxygenation at some centres

Prevention

- in utero: careful monitoring
- suctioning of the oro/nasopharynx after delivery of the head is no longer recommended
- at birth: intubate and suction below cords if infant is depressed
- note: presence of meconium staining alone is NOT an indication for tracheal suctioning
- if the infant is vigorous, intubation, and suctioning of lower airway is unnecessary

Pneumonia

- see *Pediatric Respiriology*, P91
- consider in infants with prolonged or premature rupture of membranes (PROM), maternal fever, or if mother GBS positive
- suspect if infant exhibits temperature instability, WBC low or left-shifted
- symptoms may be non-specific
- CXR: hazy lung + distinct infiltrates (may be difficult to differentiate from RDS)

Diaphragmatic Hernia

- developmental defect of diaphragm causing herniation of abdominal organs into thorax
- results in pulmonary hypoplasia on affected and contralateral side
- if resuscitation required at birth, DO NOT mask-bag because air will enter stomach and further compress lungs; infant requires endotracheal intubation

Clinical Presentation

- respiratory distress, cyanosis
- scaphoid abdomen and barrel-shaped chest
- affected side dull to percussion and breath sounds absent, may hear bowel sounds instead
- heart sounds shifted to contralateral side
- asymmetric chest movements, trachea deviated away from affected side
- may present outside of neonatal period
- often associated with other anomalies (cardiovascular, CNS lesions)
- CXR: portion of GI tract in thorax (usually left side), displaced mediastinum

Treatment

- surgery

Bronchopulmonary Dysplasia (BPD)

- also known as chronic lung disease (CLD)
- clinically defined as O₂ requirement at 28 days/36 wks GA and abnormal CXR findings (lung opacification, then cysts with sites of over distension and atelectasis, appears spongy)
- damage to developing lungs due to prolonged intubation/ventilation with high pressures and high O₂ concentration, often in preterm infants
- injury occurs due to high tidal volumes, oxygen toxicity, inflammation and infection
- chronic respiratory failure may lead to pulmonary hypertension, poor growth, and right-sided heart failure

Treatment

- no good treatments
- gradual wean from ventilator, optimize nutrition
- dexamethasone may help decrease inflammation and encourage weaning, however use of dexamethasone is associated with increased risk of adverse neurodevelopmental outcome so indications for use are limited

Prognosis

- patients with BPD continue to have significant impairment and deterioration in lung function late into adolescence
- studies show an inverse relationship between FEV₁ at school age and duration of supplemental oxygen
- some lung abnormalities may persist into adulthood including: airway obstruction, airway hyperreactivity, and emphysema
- associated with increased risk of adverse neurodevelopmental outcome

Hypoglycemia

- glucose <2.6 mmol/L (40 mg/dL)

Etiology

- decreased carbohydrate stores (premature, IUGR)
- infant of a diabetic mother (IDM): maternal hyperglycemia → fetal hyperglycemia and hyperinsulinism → hypoglycemia in the newborn infant because of high insulin levels
- sepsis
- endocrine: hyperinsulinism due to islet cell hyperplasia (e.g. Beckwith-Wiedemann syndrome), panhypopituitarism
- inborn errors of metabolism: fatty acid oxidation defects, galactosemia

Clinical Findings

- signs often non-specific and subtle: lethargy, poor feeding, irritability, tremors, apnea, cyanosis, seizures

Management

- identify and monitor infants at risk (pre-feed blood glucose checks)
- begin oral feeds within first few hours of birth
- if hypoglycemic, provide glucose IV (D10, D12.5)
- if persistent hypoglycemia (past day 3), hypoglycemia unresponsive to IV glucose, and/or no predisposing cause for hypoglycemia, send the following “critical bloodwork” during an episode of hypoglycemia:
 - insulin
 - cortisol
 - growth hormone (GH)
 - beta-hydroxybutyrate
 - lactate
 - ammonia
 - free fatty acids (FFAs)
 - ABG
- treat hyperinsulinism with glucagon and diazoxide



Jaundice



Jaundice is very common – 60% of term newborns develop visible jaundice.

- jaundice visible at serum bilirubin levels of 85-120 $\mu\text{mol/L}$ (5-6 mg/dL)
- look at sclera, mucous membranes, palmar creases, tip of nose, frenulum
- jaundice more severe/prolonged (due to increased retention of bilirubin in the circulation) with:
 - prematurity
 - acidosis
 - hypoalbuminemia
 - dehydration



Jaundice in the first 24 hours and conjugated hyperbilirubinemia are always pathological.

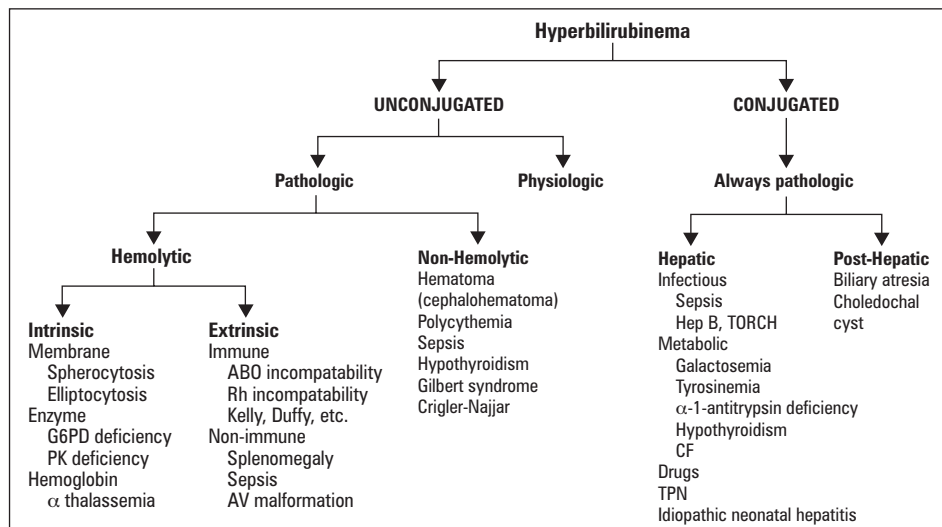


Figure 6. Approach to Neonatal Hyperbilirubinemia

PHYSIOLOGIC JAUNDICE

Epidemiology

- term infants: onset 2-3 days of life, resolution by 7 days of life
- premature infants: higher peak and longer duration

Pathophysiology

- increased hematocrit and decreased RBC lifespan
- immature glucuronyl transferase enzyme system (slow conjugation of bilirubin)
- increased enterohepatic circulation

Table 34. Risk Factors for Jaundice

Maternal Factors	Perinatal Factors	Neonatal Factors
Ethnic group (e.g. Asian, native American)	Birth trauma (cephalohematoma, ecchymoses)	Difficulty establishing breastfeeding
Complications during pregnancy (infant of diabetic mother, Rh or ABO incompatibility)	Prematurity	Infection
Breastfeeding		Genetic factors
		Polycythemia
		Drugs

Table 35. Causes of Neonatal Jaundice by Age

<24 hours	24-72 hours	72-96 hours	Prolonged (>1 week)
ALWAYS PATHOLOGIC	Physiologic, polycythemia	Physiologic ± breast feeding	Breast milk jaundice
Hemolytic	Dehydration	Sepsis	Prolonged physiologic jaundice in preterm
Rh or ABO incompatibility	(breastfeeding jaundice)		Hypothyroidism
Sepsis	Hemolysis		Neonatal hepatitis
GBS	G6PD deficiency		Conjugation dysfunction
Congenital infection (TORCH)	Pyruvate kinase deficiency		e.g. Gilbert syndrome,
	Spherocytosis		Crigler-Najjar syndrome
	Bruising, hemorrhage, hematoma		Inborn errors of metabolism
	Sepsis/congenital infection		e.g. galactosemia
			Biliary tract obstruction
			e.g. biliary atresia

Breastfeeding Jaundice

- common
- due to lack of milk production and subsequent dehydration, leading to exaggerated physiologic jaundice

Breast Milk Jaundice

- rare (1 in 200 breast-fed infants)
- inhibitor of glucuronyl transferase found in breast milk
- onset 7 days of life, peak at 2nd to 3rd week of life

PATHOLOGIC JAUNDICE

- must be investigated if:
 - jaundice at <24 hours of age
 - serum unconjugated bilirubin rises rapidly or is excessive for patient's age and weight (>85 µmol/L per day or >220 µmol/L before 4 days of age)
 - conjugated bilirubin >35 µmol/L (2.0 mg/dL)
 - persistent jaundice lasting beyond 1-2 weeks of age
- investigations
 - unconjugated hyperbilirubinemia:
 - ♦ hemolytic work-up: CBC, blood group (mother and infant), peripheral blood smear, Coombs test, bilirubin (conjugated, unconjugated)
 - ♦ if baby is unwell or has fever, septic work-up: CBC + differential, blood and urine cultures ± LP, CXR
 - ♦ other: G6PD screen (in males), TSH
 - conjugated hyperbilirubinemia: consider liver enzymes (AST, ALT), coagulation studies (PT, PTT), serum albumin, ammonia, TSH, TORCH screen, septic work-up, galactosemia screen (erythrocyte galactose-1-phosphate uridylyltransferase levels), metabolic screen, abdominal U/S, HIDA scan, sweat chloride

**"Bronzed" Baby in Infants with Conjugated Hyperbilirubinemia**

Phototherapy results in the production and accumulation of a toxic metabolite which also imparts a bronze hue on the baby's skin.

TREATMENT OF UNCONJUGATED HYPERBILIRUBINEMIA

- to prevent kernicterus (see below)
- breastfeeding does not need to be discontinued, ensure adequate feeds and hydration
- get lactation consultant support, mother to pump after feeds
- treat underlying causes (e.g. sepsis)
- phototherapy
 - insoluble unconjugated bilirubin is converted to excretable form via photoisomerization
 - serum bilirubin should be monitored during and immediately after therapy (risk of rebound because photoisomerization reversible when phototherapy discontinued)
 - contraindicated in conjugated hyperbilirubinemia: results in "bronzed" baby
 - side effects: hypernatremic dehydration, eye damage, skin rash, diarrhea
 - use published guidelines for initiation of phototherapy
- exchange transfusion
 - prevents toxic effects of bilirubin by removal from body
 - indications: high bilirubin levels as per published graphs based on age, weeks gestation
 - most commonly performed for hemolytic disease and G6PD

KERNICTERUS**Etiology**

- unconjugated bilirubin concentrations exceed albumin binding capacity and bilirubin enters and is deposited in the brain resulting in permanent damage (often basal ganglia or brainstem)
- incidence increases as serum bilirubin levels increase above 340 µmol/L (19.8 mg/dL)
- can occur at lower levels in presence of sepsis, meningitis, hemolysis, hypoxia, hypothermia, hypoglycemia and prematurity

Clinical Presentation

- up to 15% of infants have no obvious neurologic symptoms
- acute form
 - first 1-2 days: lethargy, hypotonia, poor feeding, high-pitched cry, emesis, seizures
 - middle of first week: hypertonia, opisthotonic posturing, fever, bulging fontanelle, pulmonary hemorrhage
- chronic form (first year and beyond)
 - hypotonia, delayed motor skills, extrapyramidal abnormalities (choreoathetoid cerebral palsy), gaze palsy, MR, sensorineural hearing loss

Prevention

- exchange transfusion

Complications

- sensorineural deafness, choreoathetoid cerebral palsy (CP), gaze palsy, mental retardation

BILIARY ATRESIA

- atresia of the extrahepatic bile ducts
- cholestasis and increased conjugated bilirubin after the first week of life
- incidence: 1/10,000-15,000 live births

Clinical Presentation

- dark urine, pale stool, jaundice (persisting for >2 weeks), abdominal distention, hepatomegaly

Diagnosis

- conjugated hyperbilirubinemia, abdominal ultrasound
- HIDA scan
- liver biopsy

Treatment

- surgical drainage procedure
- hepatoportoenterostomy (Kasai procedure most successful if before 8 weeks of age)
- usually ultimately requires liver transplantation
- vitamins A, D, E, and K, diet should be enriched with medium-chain triglycerides to ensure adequate fat ingestion

Bleeding Disorders in Neonates

Clinical Presentation

- oozing from the umbilical stump, excessive bleeding from peripheral venipuncture/heel stick sites/IV sites, large caput succedaneum, cephalohematomas (in absence of significant birth trauma), and prolonged bleeding following circumcision

Approach to Bleeding Disorders in Neonates

- 4 major categories
 1. **increased platelet destruction**
 - ♦ maternal ITP, SLE
 - ♦ neonatal alloimmune thrombocytopenia (NAIT)
 - ♦ infection
 - ♦ DIC
 - ♦ drugs
 - ♦ extensive localized thrombosis
 2. **decreased platelet production/function:**
 - ♦ bone marrow replacement
 - ♦ pancytopenia
 - ♦ Fanconi anemia
 - ♦ trisomy 13 and 18
 3. **metabolic:**
 - ♦ congenital thyrotoxicosis
 - ♦ inborn error of metabolism
 4. **coagulation factor deficiencies** (see [Hematology](#))
 - ♦ haemophilia A
 - ♦ haemophilia B
 - ♦ hemorrhagic disease of the newborn

NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (NAIT)**Pathophysiology**

- platelet equivalent of Rh disease of the newborn
- occurs when mother is negative for human platelet antigen (HPA) and fetus is positive
- development of maternal IgG antibodies against HPA antigens on fetal platelets

Epidemiology

- 1/4000-5000 live births

Clinical Features

- clinical features: petechiae, purpura, thrombocytopenia in otherwise healthy neonate
- severe NAIT can lead to intracranial bleeding

Diagnosis

- maternal and paternal platelet typing and identification of platelet alloantibodies

Treatment

- IVIG to mother prenatally, starts in second trimester; treat neonate with IVIG and transfusion of infant with washed maternal platelets or donor HPA negative platelets

AUTOIMMUNE THROMBOCYTOPENIA**Pathophysiology**

- caused by antiplatelet antibodies from maternal ITP or SLE
- passive transfer of antibodies across placenta

Clinical Presentation

- similar presentation to NAIT, but bleeding usually less severe

Treatment

- steroids to mother x 10-14 days prior to delivery or IVIG to mother before delivery
- IVIG to infant after delivery
- transfusion of infant with maternal / donor platelets only in severe cases, as antibodies will destroy transfused platelets

HEMORRHAGIC DISEASE OF THE NEWBORN

- caused by vitamin K deficiency
- factors II, VII, IX, X are vitamin K-dependent, therefore both PT and PTT are abnormal

Etiology and Clinical Presentation

- neonates at risk of vitamin K deficiency because:
 - vitamin K poorly transferred across the placenta
 - insufficient bacterial colonization of colon at birth (synthesize vit K)
 - dietary intake of vitamin K inadequate in breastfed infants

Prevention

- vitamin K IM administration at birth to all newborns

Necrotizing Enterocolitis (NEC)

- intestinal inflammation associated with focal or diffuse ulceration and necrosis
- primarily affecting terminal ileum and colon
- affects 1-5% of preterm newborns admitted to NICU

Pathophysiology

- postulated mechanism of bowel ischemia → mucosal damage, and enteral feeding providing a substrate for bacterial growth and mucosal invasion, leading to bowel necrosis or gangrene and perforation

Risk Factors

- prematurity (immature defenses)
- asphyxia, shock (poor bowel perfusion)
- hyperosmolar feeds
- enteral feeding with formula (breast milk can be protective)
- sepsis

Role of Human Milk in Extremely Low Birth Weight Infants' Risk of Necrotizing Enterocolitis or Death

J Perinatol 2009; 29(1): 57–62

Purpose: To determine if human milk (HM) intake is related to decreased risk of necrotizing enterocolitis (NEC) or death.

Study: An association between proportion of HM to total intake (enteral and parenteral), enteral intake alone and total volume during the first 14 days after birth to NEC and death was evaluated.

Patients: 1272 infants with a birth weight between 401 to 1000 g.

Main Outcome: NEC or death occurring between 14 days after birth to 120 days or hospital discharge.

Results: For each 10% increase in the proportion of HM to total intake, there was a decrease in likelihood of NEC or death (HR 0.83, 95% CI 0.72 – 0.96). Infants who developed NEC or died were more likely to receive parenteral nutrition only compared to infants who did not develop NEC or death (19 vs. 7.8%).

Summary: A reduction in the risk of NEC or death among extremely low birth weight infants was associated with HM feeding. A possible dose-dependent beneficial effect of HM is suggested in extremely low birth weight infants.

Clinical Presentation

- distended abdomen
- increased amount of gastric aspirate/vomit with bile staining
- frank or occult blood in stool
- feeding intolerance
- diminished bowel sounds
- signs of bowel perforation (sepsis, shock, peritonitis, DIC)

Investigations

- abdominal x-ray: pneumonitis intestinalis (intramural air, hallmark of NEC), free air, fixed loops, ileus, thickened bowel wall, portal venous gas
- CBC, ABG, blood culture
- high or low WBC, low platelets, hyponatremia, acidosis, hypoxia, hypercapnea

Treatment

- NPO (minimum 1 week), vigorous IV fluid resuscitation, NG decompression, supportive therapy
- TPN
- antibiotics (usually ampicillin, gentamicin ± metronidazole if risk of perforation x 7-10 days)
- serial abdominal x-rays detect early perforation
- peritoneal drain/surgery if perforation
- surgical resection of necrotic bowel and surgery for complications (e.g. perforation, strictures)

Intraventricular Hemorrhage (IVH)

- intracranial hemorrhage originating in the periventricular subependymal germinal matrix (GM)
- incidence and severity inversely proportional to GA

Risk Factors

- extreme prematurity, need for vigorous resuscitation at birth, pneumothorax, ventilated preterm infants, sudden increase in arterial blood pressure with volume expansion, hypotensive event, hypertension, RDS, fluctuating cerebral blood flow, coagulopathy

Clinical Presentation

- many infants with IVH are asymptomatic
- subtle signs: apnea, bradycardia, changes in tone or activity, altered level of consciousness
- catastrophic presentation: bulging fontanelle, drop in hematocrit, acidosis, seizures, hypotension

Classification

- Papile classification
 - Grade I: GM hemorrhage
 - Grade II: IVH without ventricular dilatation
 - Grade III: IVH with ventricular dilatation
 - Grade IV: GM hemorrhage or IVH with parenchymal extension
- parenchymal hemorrhage may also occur in the absence of intraventricular hemorrhage
- 50% of IVH occurs within 8 hours of birth; 90% occurs by day 3
- routine head ultrasound screening of all preterm infants <32 weeks gestation throughout NICU stay

Management of Acute Hemorrhage

- supportive care to maintain blood volume and acid-base status
- avoid fluctuations in blood pressure and cerebral blood flow
- follow-up with serial imaging

Prognosis

- outcome depends on grade of IVH
- short-term outcomes for severe IVH: mortality, posthemorrhagic hydrocephalus (PHH), posthemorrhagic infarction
- possible long-term major neurological sequelae: cerebral palsy, cognitive deficits, motor deficits, visual, and hearing impairment
- grades 1 and 2 hemorrhages have a relatively favourable prognosis
- greatest morbidity and mortality is seen with Grade 4 hemorrhage and PHH requiring ventriculoperitoneal shunt placement
- premature babies are also at risk of PVL (periventricular leukomalacia) – radiologically seen as cysts or ischemic areas in the periventricular white matter, also putting them at risk of adverse neurological outcome

Retinopathy of Prematurity (ROP)

- interruption in the growth of developing retinal vessels

Pathophysiology

- early vasoconstriction and obliteration of the capillary bed → repair response → neovascularisation
- retinal detachment occurs in a small percentage

Risk Factors

- association with period of high oxygen concentrations is not clear
- extreme prematurity is the most significant risk factor

Clinical Presentation

- ROP is classified by stage (I-V, with V being most severe)
- see Ophthalmology, OP41

Assessment

- ophthalmoscopic examination
 - infants with birthweight ≤ 1500 g or ≤ 30 weeks GA: starting at 4-6 weeks of chronologic age or at 32 weeks corrected age (whichever is later) with exams q2-3 weeks until retinal maturity with no disease or disease is regressing
 - infants with ROP or very immature vessels: exams q1-2 weeks

Management

- laser photocoagulation for severe prethreshold and threshold ROP
- follow-up eye examinations for myopia, strabismus, amblyopia, glaucoma, and late detachment

Prognosis

- stage I and II: 90% spontaneous regression
- stage III+: ~50% spontaneous regression
 - with treatment, incidence of poor visual outcome reduces by ~50%

Common Neonatal Skin Conditions

Table 36. Common Neonatal Skin Conditions

Neonatal Skin Conditions	Description
Vasomotor Response (Cutis Marmorata, acrocyanosis)	Transient mottling when exposed to cold; usually normal, particularly if premature
Vernix Caseosa	Soft creamy white layer covering baby at birth
Slate-grey nevus of childhood (‘Mongolian spots’)	Bluish grey macules over lower back and buttocks (may look like bruises); common in dark skinned infants
Capillary Hemangioma	Raised red lesion, which increases in size after birth and involutes; 50% resolved by 5 yrs, 90% by 9 yrs
Erythema Toxicum	Erythematous vesiculo-pustular rash, lesions disappear and reappear in minutes to hours, resolves by 2 weeks
Milia	Lesions 1-2 mm firm white pearly papules on nasal bridge, cheeks, and palate; self-resolving
Pustular Melanosis	Brown macular base with dry vesicles, seen more commonly in African American infants
Angiomatous Lesions (Salmon patch)	Transitory macular capillary hemangiomas of the eyelids and neck (“Angel Kiss” and “Stork Bite”); usually disappears with age
Neonatal Acne	Inflammatory papules and pustules mainly on face, self-resolving

Nephrology

Dehydration

Table 37. Assessment of Dehydration

Point of Assessment	Method
Volume deficit	History, physical examination
Osmolar disturbance	Serum Na
Acid-base disturbance	Blood pH, pCO ₂ , bicarbonate
Potassium	Serum K
Renal function	BUN, creatinine, urine specific gravity/osmolality, urine sediment

Table 38. Assessment of Severity of Dehydration

	Mild	Moderate	Severe
Pulse (HR)	Normal, full	Rapid	Rapid, weak
Blood Pressure (BP)	Normal	Normal-low	Shock – decreased BP
Urine Output (UO)	Decreased	Markedly decreased	Anuria
Oral Mucosa	Slightly dry	Dry	Parched
Anterior Fontanelle	Normal	Sunken	Markedly sunken
Eyes	Normal	Sunken	Markedly sunken
Skin Turgor	Normal	Decreased	Tenting
Capillary Refill	Normal (<3 sec)	Normal to increased	Increased (>3 sec)
% loss of Pre-Illness Body Weight			
<2 years	5%	10%	15%
>2 years	3%	6%	9%



Assessment of Severity of Dehydration

C BASE H₂O
Capillary refill
BP
Anterior fontanelle
Skin turgor
Eyes sunken
HR
Oral mucosa
Output of urine

Fluid and Electrolyte Therapy

Principles of Treatment

- provision of maintenance daily fluid and electrolyte requirements (see Table 39)
- PLUS replacement of deficit fluids and electrolytes (see Table 40) – 10cc per % weight loss per kg
- PLUS replacement of ongoing losses (consider urine output, bowel movements/diarrhea, fever)

Table 39. Maintenance Fluid and Electrolyte Requirements

Body Weight	100:50:20 Rule (24-hour maintenance fluids)	4:2:1 Rule (hourly rate of maintenance fluids)
1-10 kg	100 cc/kg/day	4 cc/kg/hr
11-20 kg	50 cc/kg/day	2 cc/kg/hr
>20 kg	20 cc/kg/day	1 cc/kg/hr
Electrolyte Requirements		
Na:	3 mEq/kg/day	
K:	2 mEq/kg/day	
Cl:	3 mEq/kg/day	

Table 40. Correction of Fluid and Electrolyte Deficits

Dehydration ¹	Rate
Isotonic (80%)	1/2 total replacement over 1st 8 hours, then 1/2 over 16 hours
Hypotonic ² (5%) (Na < 130 mmol/L)	If Na > 105, correct as above If Na < 105, correct by 20 mmol/L maximum over 0.5-4 hours with hypertonic saline
Hypertonic (15%) (Na > 150 mmol/L)	Correct over 48-72 hours Do not allow serum Na to drop faster than 10-15 mmol/L/day ³

Note:

¹For all types of dehydration, H₂O for 5% dehydration = 50mL/kg; for 10% dehydration = 100 mL/kg

²To calculate exact deficit: Na deficit = ([Na]target – [Na]actual) x body weight (kg) x total body water (L)

³To lower serum Na by a predictable amount, remember: 4 mL/kg of free H₂O lowers serum Na by 1 mmol/L



4:2:1 Rule

4 cc/kg/hr for first 10 kg
 2 cc/kg/hr for 10-20 kg
 1 cc/kg/hr for >20 kg

Common IV Fluids

- first month of life: D5W/0.2 NS + 20 mEq KCl/L (only add KCl if voiding well)
- children: D5W/0.9 NS + 20 mEq KCl/L or D5W/0.45 NS + 20 mEq KCl/L
- NS: as bolus to restore circulation in dehydrated children

Common Renal Diseases

Table 41. Common Manifestations of Renal Disease

Neonate	Differential Diagnosis
Flank Mass	Dysplasia, polycystic disease, hydronephrosis, tumour
Hematuria	Asphyxia, malformation, trauma, renal vein thrombosis
Anuria/oliguria	Agenesis, obstruction, asphyxia
Child and Adolescent	Differential Diagnosis
Cola/red-coloured urine	Hemoglobinuria (hemolysis) Myoglobinuria (rhabdomyolysis) Hematuria (e.g. glomerulonephritis), pigmenturia
Gross Hematuria	Glomerulonephritis, benign hematuria, trauma, cystitis, tumour, stones
Edema	Nephrotic syndrome, nephritis, acute/chronic renal failure (also consider cardiac or liver disease)
Hypertension	Acute glomerulonephritis, renal failure, dysplasia (also consider coarctation of aorta, drugs, endocrine causes)
Polyuria	DM, central and nephrogenic diabetes insipidus, hypercalcemia, polyuric renal failure
Oliguria	Dehydration, acute tubular necrosis (ATN), interstitial nephritis
Urgency	Urinary tract infection (UTI), vaginitis

Hematuria

- definition: ≥ 5 RBC/hpf, in three consecutive centrifuged urine samples
- 0.5-2% prevalence of asymptomatic microscopic hematuria in school-aged children
- history of prior acute infection (upper respiratory, skin or GI)
- family history: dialysis, transplant, SLE, familial hematuria
- physical exam: BP, edema, rashes, arthritis

Etiology

- nephrologic
 - glomerular disease
 - ♦ recurrent gross hematuria: IgA nephropathy, benign familial hematuria, Alport syndrome
 - ♦ post-streptococcal GN, lupus nephritis, HSP, HUS, Goodpasture disease (rare in childhood)
 - tubulointerstitial: ATN, interstitial nephritis, pyelonephritis, hypercalciuria
- infection: bacterial, TB, viral, UTI, pyelonephritis
- hematologic: coagulopathies, thrombocytopenia, sickle cell disease or trait, renal vein thrombosis
- nephrolithiasis
- anatomic abnormalities: congenital, trauma, polycystic kidneys, vascular abnormalities, tumours (Wilms)
- other: exercise, drugs



Causes of Coloured Urine with Negative Dipstick

URINE BLEAD

Urates
Rifampin
Ibuprofen
Nitrofurantoin
Exogenous (food colouring)
Beets
Lead



False Positive Dipstick (positive dipstick, but no RBCs): myoglobinuria due to rhabdomyolysis, hemoglobinuria due to intravascular hemolysis or coagulation.

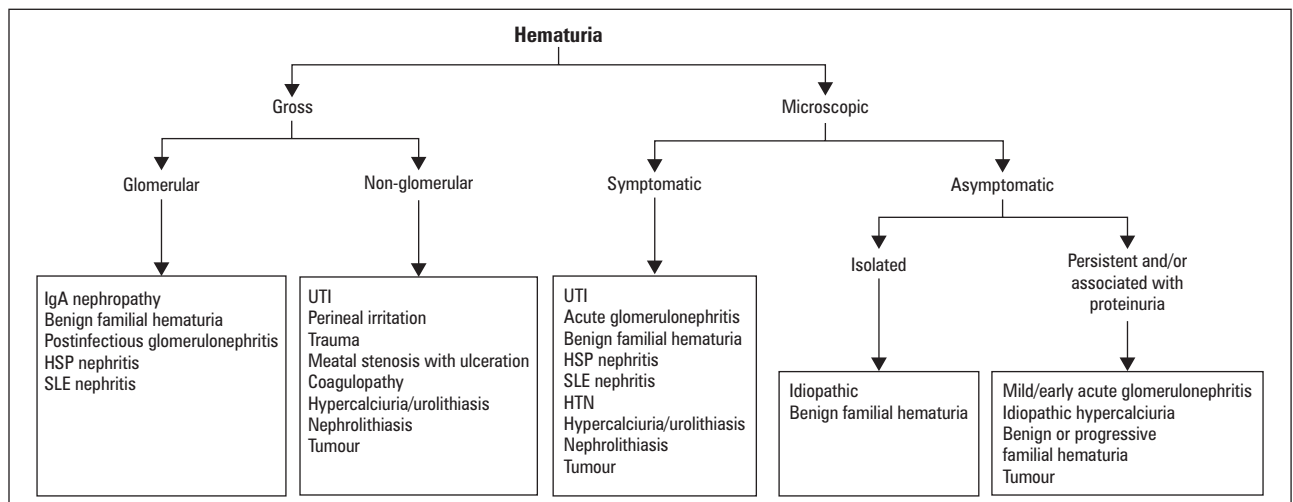


Figure 7. Approach to Hematuria in Children/Adolescents

Investigations

- CBC, urine dip and culture, creatinine, BUN, 24-hr urine collection for creatinine and protein, Ca, serum C3 and C4 level
- if suspected postinfectious glomerulonephritis: antistreptolysin O titer, ANA, throat swab
- if above do not yield a diagnosis, consider U/S ± Doppler to rule out structural anomalies
- treat underlying cause if applicable
 - supportive treatment (e.g. antihypertensives, fluid restriction, dietary modifications)
 - referral to pediatric nephrologist
 - may warrant renal biopsy depending on findings



Proteinuria

- a small amount of protein is found in the urine of healthy children $<4 \text{ mg/m}^2/\text{h}$ or $<100 \text{ mg/m}^2/\text{d}$
- definition
 - qualitative: 1+ in dilute, 2+ in concentrated urine (specific gravity >1.015)
 - quantitative: $>4 \text{ mg/m}^2/\text{h}$ on timed urine ($>40 \text{ mg/m}^2/\text{h}$ is nephrotic range)
- urine dipstick is the least accurate (false positives if urine pH >8 or SG >1.025)
- protein/creatinine ratio on spot urine is more accurate (normal <0.5 if 6 mo–2 yrs; <0.2 if over 2 yrs)
- 24-hour protein is the most accurate (normal $<100 \text{ mg/m}^2/\text{day}$)
- microalbuminuria assesses risk of progressive glomerulonephropathy in diabetes (normal $<30 \text{ mg albumin/gram creatinine}$ on first morning void)
- progressive proteinuria is the best predictor of renal disease
- transient proteinuria: due to fever ($>38.3^\circ\text{C}/101^\circ\text{F}$), dehydration, exercise, seizures, stress
- persistent proteinuria ($\geq 1+$ on dipstick)
 - orthostatic (more common in adolescents – usually benign): elevated protein excretion when upright and normal when recumbent; rarely exceeds $1 \text{ g/m}^2/\text{d}$
 - glomerular (e.g. nephrotic syndrome, glomerulonephritis)
 - tubulointerstitial (e.g. Fanconi syndrome, ATN)
 - structural abnormalities of urinary tract (e.g. hydronephrosis)

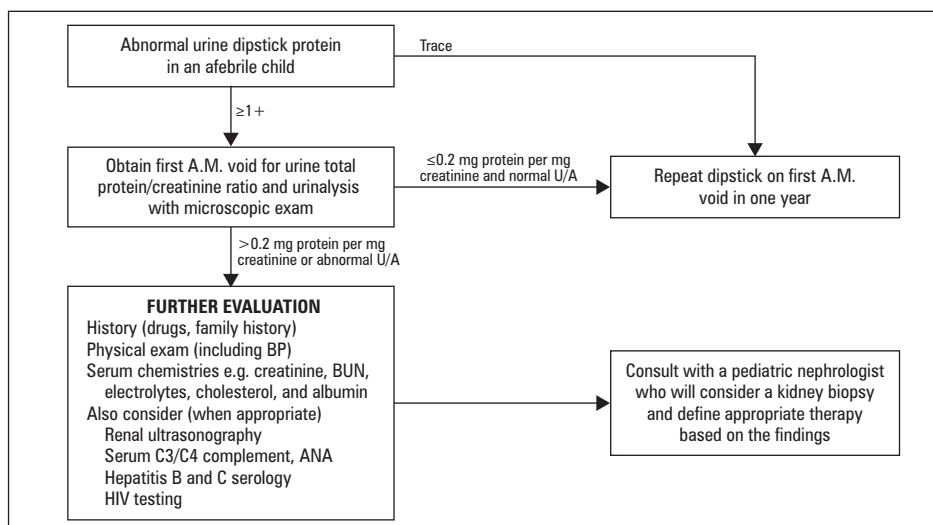


Figure 8. Evaluation of Persistent Proteinuria in Children/Adolescents

Adapted from Hogg R.J. et al. *Paediatrics* 2000; 105:1242-49.



Hemolytic Uremic Syndrome (HUS)

Epidemiology

- most common cause of acute renal failure in children
- more common from 6 months to 4 years of age

Pathophysiology

- *E. coli* O157:H7 verotoxin (“hamburger disease”) or shiga toxin
 - toxin binds, invades and destroys colonic epithelial cells, causing bloody diarrhea
 - toxin enters the systemic circulation, attaches, and injures endothelial cells (especially in kidney) causing a release of endothelial products (e.g. von Willebrand factor, platelet aggregating factor)
 - form platelet/fibrin thrombi in multiple organ systems (e.g. renal, pancreas, brain) resulting in thrombocytopenia
 - RBCs are forced through occluded vessels resulting in fragmented RBC (schistocytes) and removed by the reticuloendothelial system (hemolytic anemia)
 - other, rare forms of HUS in childhood are due to bacteria (e.g. *S. pneumoniae*), viruses, familial inheritance, or drugs

Clinical Presentation

- triad: acute renal failure, thrombocytopenia, microangiopathic hemolytic anemia
- initial presentation of abdominal pain and diarrhea, followed by bloody diarrhea
- within 5-7 days the patient begins to show signs of anemia, thrombocytopenia and renal insufficiency
 - history: weakness, lethargy, oliguria
 - physical exam: pallor, jaundice (hemolysis), edema, petechiae, hypertension

Investigations

- CBC, platelets, blood smear, urinalysis, BUN, creatinine, stool culture and shigella toxin assay

Treatment

- supportive treatment; nutritional support; monitor electrolytes; dialysis if electrolyte abnormality cannot be corrected, fluid overload, or BUN >100 mg/dL; PRBC for symptomatic anemia
- steroids not helpful; antibiotics not indicated

Prognosis

- 5-10% mortality, 10-30% kidney damage

Nephritic Syndrome

- acute, subacute or chronic
 - hematuria with RBC casts, proteinuria (<50 mg/kg/day, not nephrotic-range), azotemia, hypertension
 - renal failure (oliguria)

POST-STREPTOCOCCAL GLOMERULONEPHRITIS**Risk Factors**

- most common in children, aged 4 to 8 year old, M > F
- occurs 1-3 weeks following group A beta-hemolytic streptococcal infection of skin or throat

Pathophysiology

- antigen-antibody mediated complement activation
- diffuse, proliferative glomerulonephritis

Diagnosis

- elevated serum antibody titres against strep antigens (ASOT, anti DNaseB)

Prognosis

- 95% of children recover completely within 1-2 weeks
- 5-10% have persistent hematuria

Management

- symptomatic treatment: fluid restriction, antihypertensives, diuretics
- in severe cases: hemodialysis or peritoneal dialysis may be necessary
- eradication of infection (penicillin or erythromycin)

Table 42. Major Causes of Acute Glomerulonephritis

	Decreased C3	Normal C3
Renal	Post-infectious GMN Membranoproliferative • Type I (50-80%) • Type II (>80%)	IgA Nephropathy Idiopathic rapidly progressive GMN Anti-GBM disease
Systemic	SLE SBE Shunt nephritis Cryoglobulinemia	Polyarteritis nodosa Wegener's granulomatosis Goodpasture's syndrome Henoch-Schönlein purpura (HSP)

Nephrotic Syndrome

Clinical Presentation

- severe proteinuria (>50 mg/kg/day or >40 mg/m²/hr)
- hypoalbuminemia <20 g/L (<2.0 g/dL)
- edema (usually first sign; initially see facial swelling, especially periorbital, and pretibial edema)
- hyperlipidemia >5.17 mmol/L (200 mg/dL)
- secondary findings: hypocalcemia, hyperkalemia, hyponatremia, hypercoagulability (decreased PTT)

**Nephritic Syndrome****PHAROH**

Proteinuria (<50 mg/kg/d)
Hematuria
Azotemia
RBC casts
Oliguria
Hypertension

**PALE**

Proteinuria (>50 mg/kg/d)
HypoAlbuminemia (<20 g/L)
HyperLipidemia
Edema

Etiology

Primary Nephrotic Syndrome

- minimal change disease (MCD) (76%)
 - peak occurrence between 2-6 years of age, more common in boys than girls (2:1)
 - often treated empirically with steroids without kidney biopsy, 90% steroid responsive
- membranous glomerulonephritis (8%)
- focal segmental glomerular sclerosis (FSGS) (7%)
- membranoproliferative glomerulonephritis (5%)

Secondary Nephrotic Syndrome

- vasculitis
- infections (e.g. hepatitis B and C, syphilis, HIV)
- medications (e.g. captopril, penicillamine, NSAIDs, anticonvulsants)
- malignancy
- hereditary (e.g. sickle cell disease, Alport syndrome)
- metabolic, inflammatory (e.g. lupus nephropathy, rheumatoid arthritis)

Complications

- risk of infections (e.g. spontaneous peritonitis, cellulitis, sepsis)
- hypercoagulability due to decreased intravascular volume and antithrombin III depletion (pulmonary embolism, renal vein thrombosis)
- side effects of drugs (diuretics, steroids, immunosuppressants)
- hypotension, shock, renal failure

Investigations

- to rule out secondary causes of NS: serum complement levels, BUN, Cr, serum chemistries, ANA, antistreptolysin O titre, in certain cases HIV, Hep B/C and syphilis titers
- consider kidney biopsy if
 - HTN (higher risk of FSGS), steroid resistant, frequent relapses (>2 relapses in 6 month period), low serum complement, severely decreased renal function
 - presentation before first year of life (high likelihood of congenital nephrotic syndrome)
 - presentation after 10 years of age to rule out more serious renal pathology than MCD

Management

- salt and water restriction, diuretic may be required
- optimal nutrition, including high-quality protein
- daily weights to assess therapeutic progress
- varicella antibody titre if not immune
- pneumococcal vaccine after remission (avoid live vaccines)
- initial treatment of MCD
 - oral prednisone (or equivalent) 60 mg/m²/day in divided doses (max. dose 80 mg/day) for up to 12 weeks
 - a negative tuberculin skin test should be performed before starting steroid medications
 - a measurable decrease in protein excretion may take at least 7 to 10 days following initiation of treatment, and proteinuria clears by third week of oral prednisone
 - up to 2/3 of patients experience relapses
- if unresponsive to steroids, frequent relapses, or steroid-resistant (proteinuria continues beyond 3 months)
 - consider renal biopsy or treat with cytotoxic agent (e.g. cyclophosphamide or chlorambucil), immunomodulating agents such as levamisole and cyclosporine A, and high-dose pulse corticosteroid with guidance of a pediatric nephrologist



Hypertension in Childhood

Etiology

- consider white coat hypertension for all ages

Table 43. Etiology of Childhood Hypertension by Age Group

System	<1 year	1-6 years	7-12 years	>13 years
Cardiovascular	Coarctation of the aorta	Neuroblastoma Coarctation of aorta	Essential hypertension	Essential hypertension
Endocrine Metabolic	Hypercalcemia	Wilm's tumour	Endocrine causes (hyperthyroid, hyperparathyroid, Cushing, primary hyperaldosteronism)	Endocrine cause
Renal	Renal artery/vein thrombosis Congenital renal disease	Renal artery stenosis Renal parenchymal disease	Renal parenchymal disease abnormalities of renal vasculature	Renal parenchymal disease
Respiratory	Bronchopulmonary dysplasia			

Table 44. 95th Percentile Blood Pressures (mmHg)

Age (Years)	Female		Male	
	50th Percentile for Height	75th Percentile for Height	50th Percentile for Height	75th Percentile for Height
1	104/58	105/59	102/57	104/58
6	111/73	112/73	114/74	115/75
12	123/80	124/81	123/81	125/82
17	129/84	130/85	136/87	138/88

Adapted from Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents working group report from the National High Blood Pressure Education Program.

Investigations

- labs
 - urine dipstick for blood and protein (suggests renal disease)
 - urine catecholamines and their metabolites (may suggest pheochromocytoma)
 - electrolytes, creatinine, catecholamines, renin, aldosterone
- imaging
 - echocardiography
 - abdominal U/S
 - doppler studies, angiography, or radionuclide imaging of renal arteries

Management

- treat underlying cause
- weight reduction, reduction in salt intake, exercise
- first line antihypertensives are thiazide diuretics, but none of the antihypertensives have been formally studied in children
- referral to specialist
- medications used in hypertensive emergencies: hydralazine, labetalol, sodium nitroprusside
- assessment and management of end organ damage (e.g. retinopathy, LVH)



Pediatric Blood Pressure Calculation

$$\text{sBP} = \text{age} \times 2 + 90$$

$$\text{dBP} = 2/3 \times \text{sBP}$$

Neurology

Seizure Disorders

- see [Neurology](#), N8

Differential Diagnosis of Seizures in Children

- benign febrile seizure (most common)
- hypoxic ischemic encephalopathy ("asphyxia")
- intracranial hemorrhage, trauma
- metabolic causes (e.g. hypoglycemia, hypocalcemia, hyponatremia)
- CNS infection
- idiopathic epilepsy and epileptic syndromes
- neurocutaneous syndromes
- CNS tumour
- arteriovenous malformation
- ingestions/drug withdrawal
- rule out conditions that mimic seizure:
 - breath holding
 - night terror
 - benign paroxysmal vertigo
 - narcolepsy
 - pseudoseizure
 - syncope
 - tic
 - hypoglycemia
 - TIA

Investigations

- CBC, electrolytes, calcium, magnesium, glucose
- toxicology screen if indicated
- EEG, CT and LP if indicated
 - EEG may be indicated for first-time non-febrile seizure
 - EEG/CT not indicated for benign febrile seizures recurrence risk or to determine seizure type or epileptic syndrome



Heart problems, such as long QT syndrome and hypertrophic cardiomyopathy, are often misdiagnosed as epilepsy. Include cardiac causes of syncope in your differential diagnosis, particularly when the episodes occur during physical activity.

CHILDHOOD EPILEPTIC SYNDROMES

Infantile Spasms

- onset 4-8 months
- brief, repeated symmetric contractions of neck, trunk, extremities (flexion and extension) lasting 10-30 seconds
- occur in clusters; often associated with developmental delay
- 20% unknown etiology; may have good response to treatment
- 80% due to metabolic or developmental abnormalities, encephalopathies, or are associated with neurocutaneous syndromes; these have poor response to treatment
- can develop into West syndrome (infantile spasms, psychomotor developmental arrest, and hyperarrhythmia) or Lennox Gastaut
- typical EEG: hypsarrhythmia (high voltage slow waves, spikes and polyspikes, background disorganization)
- treatment: ACTH, vigabatrin, benzodiazepenes

Ketogenic Diet for Epilepsy

Cochrane Database of Systematic Reviews 2003; Issue 3

This systematic review found no randomized trials evaluating the use of ketogenic diet.

Reviewers' conclusions: Observational studies suggest that a ketogenic diet may decrease seizure frequency. The ketogenic diet is a possible option for those with difficult epilepsy on multiple antiepileptic drugs.

Lennox-Gastaut

- onset commonly 3-5 years of age
- characterized by triad of 1) multiple seizure types, 2) diffuse cognitive dysfunction and 3) slow generalized spike and slow wave EEG
- seen with underlying encephalopathy and brain malformations
- treatment: valproic acid, benzodiazepines and ketogenic diet; however, response often poor

Juvenile Myoclonic Epilepsy (Janz)

- adolescent onset (12-16 years of age); autosomal dominant with variable penetrance
- myoclonus particularly in morning; frequently presents as generalized tonic-clonic seizures
- typical EEG: 3.5-6 Hz irregular spike and wave, increased with photic stimulation
- requires lifelong treatment (valproic acid); prognosis excellent

Childhood Absence Epilepsy

- multiple absence seizures per day that may generalize in adolescence or resolve spontaneously
- peak age of onset 6-7, F>M, strong genetic predisposition
- each seizure is less than 30 seconds, no post-ictal state, may have multiple seizures per day
- typical EEG: 3/sec spike and wave
- treatment: valproic acid or ethosuximide

Benign Focal Epilepsy of Childhood with Rolandic/Centrotemporal Spikes

- onset peaks at 5-10 years of age, 16% of all non-febrile seizures
- focal motor seizures involving tongue, mouth, face, upper extremity usually occurring in sleep-wake transition states
- remains conscious, but aphasic post-ictally
- remits spontaneously in adolescence; no sequelae
- typical EEG: repetitive spikes in centrotemporal area with normal background
- treatment: frequent seizures controlled by carbamazepine, no medication if infrequent seizures

Treatment

- anticonvulsants often initiated if >2 unprovoked afebrile seizures within 6-12 months
 1. initiate: treatment with drug appropriate to seizure type
 2. optimize: start with one drug and increase dosage until seizures controlled
 3. if no effect, switch over to another before adding a second anticonvulsant
 4. continue anticonvulsant treatment until patient free of seizures for 2 years or more, then wean medications over 4-6 months
- ketogenic diet (high fat diet) – used in patients who do not respond to polytherapy or who do not wish to take medication (valproic acid contraindicated in conjunction with ketogenic diet because may increase hepatotoxicity)
- education for patient and parents
 - privileges and precautions in daily life (e.g. buddy system, showers instead of baths)
- legal obligation to report to Ministry of Transportation if patient wishes to drive

Generalized and Partial Seizures

- see [Neurology](#), N8

Febrile Seizures

Epidemiology

- most common cause of seizure in children
- 3-5% of all children, M>F
- age 6 months-6 years

Clinical Presentation

- thought to be associated with initial rapid rise in temperature
- no evidence of CNS infection/inflammation before or after seizure
- no history of non-febrile seizures

Table 45. Comparison of Simple and Complex Febrile Seizures

Simple/Benign (70-80%)	Complex/Atypical (20-30%)
Duration <15 minutes (95% <5 minutes)	Any one of:
Generalized tonic-clonic	Duration >15 minutes
No recurrence in 24-hour period	Focal onset or focal features during seizure
No neurological impairment or developmental delay before or after seizure	Recurrent seizures (>1 in 24-hour period)
	Previous neurological impairment or neurological deficit after seizure

Risk Factors for Recurrence

- 33% chance of recurrence, 75% recur within 1 year
 - 50% chance of recurrence if <1 year of age
 - 28% chance of recurrence if >1 year of age
- family history of febrile seizures or epilepsy
- risk factors include developmental or neurological abnormalities of child prior to seizures, family history of non-febrile seizures, and an atypical initial seizure, multiple simple febrile seizures

Workup

- history: determine focus of fever, description of seizure, meds, trauma history, development, family history
- exam: LOC, signs of meningitis, neurological exam
- septic work-up including LP if suspecting meningitis (if child <12 months, strongly consider doing an LP; if child is 12-18 months, consider including an LP; if child >18 months, do LP if meningeal signs)
- if simple febrile seizure, investigations unnecessary except for determining focus of fever
- EEG not warranted unless complex febrile seizure or abnormal neurologic findings

Management

- counsel and reassure patient and parents (febrile seizures do not cause brain damage, very small risk of developing epilepsy: 9% in child with multiple risk factors; 2% in child with febrile simple seizures compared to 1% in general population)
- antipyretics (e.g. acetaminophen) and fluids for comfort (neither prevent seizure)
- prophylaxis not recommended
- if high risk for recurrent or prolonged seizures, have rectal or sublingual lorazepam at home (danger of lorazepam is that it may hide signs of a CNS infection)
- treat underlying cause of fever (e.g. otitis media)



If a febrile seizure lasts >15 minutes, suspect meningitis or a toxin.

Randomized, Controlled Trial of Ibuprofen Syrup Administered During Febrile Illnesses to Prevent Febrile Seizure Recurrences

van Stuijvenberg M. et al.
Pediatrics 1998; 102(5):E51

Purpose: To assess the efficacy of intermittent antipyretic treatment in the prevention of febrile seizure recurrences.

Study: Double blind RCT with 220 children and 2 year follow-up.

Participants: Children age 1-4 with febrile seizure within the last month, and at least one risk factor for febrile seizure recurrence: either family history of febrile seizures, previous recurrent febrile seizures, temperature <40.0 C at the initial seizure, or multiple type initial seizure.

Interventions: Ibuprofen 5 mg/kg every 6 hours during fever (rectal T >38.4 C) or placebo.

Main Outcomes: First recurrence of febrile seizure.

Results: On an intention-to-treat analysis, the 2-year recurrence probabilities were 32% in the ibuprofen group and 39% in the placebo group, with a non-significant risk reduction of 0.9 (95% CI, 0.6-1.5).

Conclusions: There is no evidence to support intermittent antipyretic therapy in preventing febrile seizures.

Recurrent Headache

- see Neurology, N39

Assessment

- if unremarkable history and neurological and general physical exam is negative, likely diagnosis is migraine or tension-type headache
- obtain CT or MRI if history or physical reveals red flags
- inquire about level of disability, academic performance, after-school activities

Differential Diagnosis

- primary headache: tension, migraine, cluster
- secondary headache: see Neurology, N40

MIGRAINE

- 4-5% of school aged children
- prevalence F:M = 2:1 after puberty
- heterogeneous autosomal dominant inheritance with incomplete penetrance (majority of patients have a positive family history)

Types

- common (without aura) – most common in children, associated with intense nausea and vomiting
- classic (with aura)
- complicated: e.g. basilar, ophthalmoplegic, confusional, hemiplegic

**Headache – Red Flags**

New headache

Worst headache of their lives

Acute onset

Focal neurological deficits

Constitutional symptoms

Worse in morning

Worse with bending over, coughing, straining

Change in level of consciousness

Clinical Features

- in infancy, symptoms include spells of irritability, sleepiness, pallor, and vomiting
- in a young child, symptoms include periodic headaches with nausea and vomiting; relieved by rest
- usually unilateral throbbing headaches in kids with photophobia or phonophobia

Prognosis and Treatment

- over 50% of children undergo spontaneous prolonged remission after 10 years of age
- early analgesia (ibuprofen) and rest in quiet, dark room
- non-pharmacological treatment and prophylaxis: avoid triggers (poor sleep, stress, cheese, chocolate, caffeine), biofeedback techniques, exercise
- pharmacological prophylaxis: beta-blockers (e.g. propranolol), antihistamines, antidepressants (e.g. amitriptyline), calcium-channel blockers, anticonvulsants (e.g. divalproex sodium)
- children >12 years can use sumatriptan nasal spray, other tryptans

TENSION HEADACHES

- usually consists of bilateral pressing tightness anywhere on the cranium or suboccipital region, usually frontal, hurting or aching quality, non-throbbing
- lasts 30 minutes to days, waxes and wanes, may build in intensity during the day
- no nausea/vomiting, not aggravated by routine physical activity
- most children have insight into the origin of headache: poor self-image, fear of school failure
- red flags: sudden mood changes, disturbed sleep, fatigue, withdrawal from social activities, chronic systemic signs (e.g. weight loss, fever, anorexia, focal neurological signs)
- treatment
 - reassurance and explanation about how stress may cause a headache
 - rule out refractory errors in eyesight as cause of headache
 - mild analgesia (NSAIDs, acetaminophen)
 - supportive counselling

ORGANIC HEADACHES

- organic etiology often suggested with occipital headache and red flags
- with increased ICP
 - etiology: brain tumours, hydrocephalus, meningitis, encephalitis, cerebral abscess, pseudotumour cerebri, subdural hematoma
 - characteristics: diffuse early morning headaches, early morning vomiting, headache worsened by increased ICP (cough, sneeze, Valsalva); as ICP increases, headache is constant and child is lethargic and irritable
- without increased ICP
 - etiology: cerebral arteriovenous malformation (AVM), aneurysm, collagen vascular diseases, subarachnoid hemorrhage, stroke



Hypotonia

- decreased resistance to movement – “floppy baby”
- proper assessment of tone requires accurate determination of gestational age
- evaluate
 - spontaneous posture (spontaneous movement, movement against gravity, frog-leg position) important in evaluation of muscle weakness
 - joint mobility (hyperextensibility)
 - muscle bulk, presence of fasciculations
- postural maneuvers
 - traction response – pull to sit, look for flexion of arms to counteract traction and head lag
 - axillary suspension – suspend infant by holding at axilla and lifting; hypotonic babies will slip through grasp because of low shoulder girdle tone
 - ventral suspension – infant is prone and supported under the abdomen by one hand; infant should be able to hold up extremities; inverted “U” posturing demonstrates hypotonia, i.e. baby will drape self over examiner’s arms
- investigations will depend on history and physical exam
 - rule out systemic disorders
 - blood glucose
 - enhanced CT of brain
 - peripheral CK, EMG, muscle biopsy
 - chromosome analysis, genetic testing
- treatment: counsel parents on prognosis and genetic implications; refer patients for specialized care, refer for rehabilitation, OT, PT, assess feeding ability



Causes of hypotonia that respond to rapid treatment: hypokalemia, hypermagnesemia, acidemia, toxins, drugs, hypoglycemia, seizure, infection, intracranial bleeding, hydrocephalus.

Differential Diagnosis

- central
 - chromosomal (e.g. Down syndrome, Prader-Willi, Fragile X)
 - metabolic (e.g. hypoglycemia, kernicterus)
 - perinatal problems (e.g. asphyxia, ICH)
 - endocrine (e.g. hypothyroidism, hypopituitarism)
 - infections (e.g. TORCH)
 - CNS malformations
 - dysmorphic syndromes
- peripheral
 - motor neuron (e.g. spinal muscular atrophy, polio)
 - peripheral nerve (e.g. Charcot-Marie-Tooth syndrome)
 - neuromuscular junction (e.g. myasthenia gravis)
 - muscle fibres (e.g. mitochondrial myopathy, muscular dystrophy, myotonic dystrophy)

Cerebral Palsy (CP)

- a symptom complex, not a disease
- nonprogressive central motor impairment syndrome due to insult to or anomaly of the immature CNS, extent of intellectual impairment varies, presentation of the impairment changes with age
- incidence: 1.5-2.5:1,000 live births (industrialized nations)
- life expectancy is dependent on the degree of mobility and intellectual impairment, not on severity of CNS lesion

Etiology

- often obscure, no definite etiology identified in 1/3 of cases
- only 10% related to intrapartum asphyxia
- 10% due to postnatal insult (infections, asphyxia, prematurity with intraventricular hemorrhage and trauma)
- association with low birth weight babies

Clinical Presentation

Table 46. Types of Cerebral Palsy

Type	% of Total CP	Characteristics	Area of Brain Involved
Spastic	70-80%	Truncal hypotonia in 1st year Increased tone, increased reflexes, clonus Affects one limb (monoplegia), one side of body (hemiplegia), both legs (diplegia), both arms and legs (quadriplegia)	UMN of pyramidal tract Diplegia associated with periventricular leukomalacia (PVL) in premature babies Quadriplegia associated with HIE (asphyxia), associated with higher incidence of MR
Athetoid/Dyskinetic	10-15%	Athetosis (involuntary writhing movements) ± chorea (involuntary jerky movements) Can involve face, tongue (results in dysarthria)	Basal ganglia (may be associated with kernicterus)
Ataxic	<5%	Poor coordination, poor balance (wide based gait) Can have intention tremor	Cerebellum
Atonic	<5%	Marked hypotonia, hyperreflexia, severe cognitive delay	
Mixed	10-15%	More than one of the above motor patterns	

Other Signs

- swallowing incoordination – aspiration
- microcephaly (25%)
- seizures
- mental retardation, learning disabilities
- delay in motor milestones

Investigations

- may include metabolics, chromosome studies, serology, neuroimaging, EMG, EEG (if seizures), ophthalmology, audiology

Treatment

- maximize potential through multidisciplinary services; important for family to be connected with various support systems
- orthopedic management (e.g. dislocations, contractures, rhizotomy)
- management of symptoms: spasticity (baclofen, botox), constipation (stool softeners)



In neurocutaneous syndromes, the younger the child at presentation, the more likely they are to develop mental retardation.

Neurocutaneous Syndromes

- characterized by tendency to form tumours of CNS, PNS, viscera and skin

Neurofibromatosis Type I (NF-1)

- autosomal dominant but 50% are the result of new mutations
- also known as von Recklinghausen disease
- incidence 1:3000, mutation in NF1 gene on 17q11.2 (codes for neurofibromin protein)
- learning disorders, abnormal speech development, and seizures are common
- diagnosis of NF-1 requires 2 or more of
 - ≥ 6 café-au-lait spots (>5 mm if prepubertal, >1.5 cm if postpubertal)
 - ≥ 2 neurofibromas of any type or one plexiform neurofibroma
 - ≥ 2 Lisch nodules (hamartomas of the iris)
 - optic glioma
 - freckling in the axillary or inguinal region
 - a distinctive bony lesion (e.g. sphenoid dysplasia, cortical thinning of long bones)
 - a first degree relative with confirmed NF-1

Neurofibromatosis Type II (NF-2)

- autosomal dominant
- incidence 1:33 000
- characterized by predisposition to form intracranial, spinal tumours
- diagnosed when either bilateral vestibular schwannomas found, or a first-degree relative with NF-2 and either a neurofibroma, meningioma, glioma, or schwannoma
- also associated with posterior subcapsular cataracts
- treatment consists of monitoring for tumour development and surgery

Sturge-Weber Syndrome

- port-wine nevus syndrome in V1 distribution with associated angiomatous malformations of brain causing contralateral hemiparesis and hemiatrophy
- also associated with seizure, glaucoma and mental retardation

Tuberous Sclerosis

- autosomal dominant inheritance; 50% new mutations
- adenoma sebaceum (angiokeratomas on face, often in malar distribution), Shagreen patch (isolated raised plaque over lower back, buttocks), “ash leaf” hypopigmentation seen with Wood’s lamp (UV light)
- cardiac rhabdomyomas, kidney angiomyolipoma, mental retardation and seizures
- cerebral cortex tubers (areas of cerebral dysplasia); subependymal nodules (SEN) may evolve into giant cell astrocytomas (may cause obstructive hydrocephalus)
- calcifications within the SEN are seen on CT, MRI (especially around the foramen of Munroe)
 - these may obstruct the foramen and cause hydrocephalus

Acute Disseminated Encephalomyelitis (ADEM)

Epidemiology

- median age of onset 5-8 years
- male predominance (M:F – 2:1)
- annual incidence in North America is estimated to be 0.4 per 100,000 children <20 yrs of age

Pathophysiology

- immune-mediated inflammatory disorder of the CNS
- characterized by a widespread demyelination predominantly affecting the white matter of the brain and spinal cord (similar to Multiple Sclerosis)
- usually preceded by a viral infection or vaccination, and is therefore commonly categorized as either post-vaccination or post-infectious
- absence of clear precedent event has been reported in 26% of patients

Clinical Presentation

- often occurs 2 days to 4 weeks after a clinically evident infection or vaccination
- clinical course is rapidly progressive and usually develops over hours to maximum deficits within days
- headache, nausea, vomiting
- pyrexia/malaise
- rapid onset encephalopathy
- multifocal deficits
- seizures
- pyramidal syndrome
- cerebellar ataxia
- brainstem involvement

Investigations

1. LP → CSF showing variable pleocytosis and oligoclonal banding
2. MRI → large, multifocal, poorly marginated regions of demyelination affecting bilateral subcortical white matter, and deep grey matter (thalamus, basal ganglia); lesions show complete or partial resolution on follow-up, with absence of new clinically silent lesions

Treatment

- high dose corticosteroids and supportive measures

Prognosis

- favourable, though some residual deficits often exist

Oncology

- cancer is second most common cause of death in children after 1 year of age (injuries are first)
- cause is rarely known, but increased risk with
 - chromosomal syndromes
 - prior malignancy
 - neurocutaneous syndromes
 - immunodeficiency syndromes
 - family history
 - exposure to radiation, chemicals, biologic agents
- leukemias are the most common type of pediatric malignancy (40%), followed by brain tumours (20%), and lymphomas (15%)
- some malignancies are more prevalent in certain age groups
 - newborns: neuroblastoma, other embryonal tumours e.g. Wilms' tumour (nephroblastoma), retinoblastoma
 - infancy and childhood: leukemia, neuroblastoma, Wilms' tumour, retinoblastoma
 - adolescence: lymphoma, gonadal tumours, bone tumours
- unique treatment considerations because radiation, chemotherapy, and surgery can impact growth and development, endocrine function and fertility
- most children do survive – treatments have led to remarkable improvements in overall survival and cure rates for many pediatric cancers

Leukemia

- see Hematology, H38, H41, H46

Epidemiology

- mean age of diagnosis 2-5 years but can occur at any age
- heterogeneous group of diseases:
 - acute lymphoblastic leukemia (ALL) (75%)
 - acute myeloblastic leukemia (AML) (10%)
 - chronic myelogenous leukemia (CML) (5%)
 - unclear type (10%)
- children with Down syndrome are 15 times more likely to develop leukemia

Etiology

- mostly unknown; retrovirus (HTLV) may be associated with T-cell leukemia

Clinical Presentation

- infiltration of leukemic cells into bone marrow results in bone pain, and subsequent bone marrow failure (anemia, neutropenia, thrombocytopenia)
- infiltration into tissues results in: lymphadenopathy, hepatosplenomegaly, CNS manifestations
- fever, fatigue, weight loss

Prognosis

- 80-90% 5-year event-free survival for ALL, 50% for AML

Lymphoma

- see [Hematology](#), H42

Hodgkin's Lymphoma

- incidence is bimodal: peaks at age 15-34 and 50+
- similar to adult Hodgkin's
- most common presentation is persistent, painless, firm, cervical or supraclavicular lymphadenopathy
- can present as persistent cough (secondary to mediastinal mass) or less commonly as splenomegaly, axillary or inguinal lymphadenopathy
- constitutional symptoms (B symptoms) in 30% of children

Non-Hodgkin's Lymphoma

- incidence peaks 7-11 years
- generally categorized into lymphoblastic, large cell, and Burkitt's/Burkitt's-like lymphoma
- rapidly growing tumour with distant metastases (unlike adult non-Hodgkin's lymphoma)
- signs and symptoms related to disease site
 - most commonly abdomen, chest (mediastinal mass), head and neck region

Etiology

- mostly unknown; EBV associated with African Burkitt's lymphoma

Treatment

- aggressive multidrug chemotherapy with radiation and surgery to debulk large tumour masses
- 80-90% 5-year survival in Hodgkin's; 50-75% in non-Hodgkin's

Brain Tumours

- see [Neurosurgery](#), NS9, NS39
- classified by location and histology
- location: 60% infratentorial (cerebellum, midbrain, brainstem) versus supratentorial
- histology: glial (cerebellar astrocytomas most common), primitive neuroectodermal (medulloblastoma), neuronal, pineal

Clinical Presentation

- infratentorial: increased ICP (obstruction of 4th ventricle), vomiting, morning headache, increased head circumference, CN VI palsy, upward-gazing eyes, ataxia, cranial nerve palsies
- supratentorial: focal deficits, seizures, long tract signs, visual field defects
- evaluation
 - history, physical exam including complete neurological exam
 - CT and/or MRI of head

Wilms' Tumour (Nephroblastoma)

- usually diagnosed between 2 and 5 years of age
 - most common primary renal neoplasm of childhood
 - M=F
 - 5-10% of cases both kidneys are affected (simultaneously or in sequence)
- differential diagnosis
 - hydronephrosis, polycystic kidney disease, renal cell carcinoma, neuroblastoma

Clinical Presentation

- 80% present with asymptomatic, unilateral abdominal mass
- may also present with hypertension, gross hematuria, abdominal pain, vomiting
- may have pulmonary metastases at time of primary diagnosis (respiratory symptoms)

Associated Congenital Abnormalities

- WAGR syndrome (Wilms' tumour, Aniridia, Genital anomalies, mental Retardation) with 11p13 deletion
- Beckwith-Wiedemann syndrome
 - characterized by enlargement of body organs, hemihypertrophy, renal medullary cysts, and adrenal cytomegaly
 - also at increased risk for developing hepatoblastoma, adrenocortical tumours, rhabdomyosarcomas, and pancreatic tumours
- Denys-Drash syndrome
 - characterized by gonadal dysgenesis and nephropathy leading to renal failure



'B Symptoms' = fever, night sweats, unexplained weight loss.

Management

- nephrectomy
- staging, chemotherapy, radiation

Prognosis

- 90% long-term survival

Neuroblastoma

Epidemiology

- most common cancer occurring in first year of life
- neural crest cell tumour arising from sympathetic tissues (neuroblasts)
 - adrenal medulla (45%)
 - sympathetic chain (25% retroperitoneal, 20% posterior mediastinal, 4% pelvis, 4% neck)

Clinical Presentation

- can originate from any site in sympathetic nervous system, presenting as mass in neck, chest or abdominal mass (most common site is adrenal gland)
- signs and symptoms of disease vary with location of tumour
 - thoracic: dyspnea, Horner's syndrome
 - abdomen: palpable mass
 - spinal cord compression
- metastases are common at presentation (>50% present with advanced stage disease)
 - usually to bone or bone marrow (presents as bone pain, limp)
 - can also present with periorbital ecchymoses, abdominal pain, emesis, fever, weight loss, anorexia, hepatomegaly, "blueberry muffin" skin nodules
- paraneoplastic: hypertension, palpitations, sweating (from excessive catecholamines), diarrhea, FTT (from VIP secretion), opsomyoclonus

Investigations

- CBC, electrolytes, LFTs, renal function tests, LDH, Ca, Mg, serum ferritin
- urine VMA, HVA levels
- CT scan of chest, abdomen and pelvis, bone scan, MIBG scan
- bone marrow analysis – neuroblastoma cells in "rosettes"
- tissue biopsy

Good Prognostic Factors

- "age and stage" are important determinants of better outcome
 - <1 year old
 - stage I, II, IV-S disease ("S" designates a "Special" classification only pertaining to infants)
- primary site: posterior mediastinum and neck
- low serum ferritin
- specific histology
- tumour cell markers
 - aneuploidy
 - absent N-myc oncogene amplification

Management

- depends on prognostic factors and may include any of the following alone or in combination: surgery, radiation, chemotherapy, bone marrow transplantation
- prognosis is often poor as it is found at an advanced stage

Rhabdomyosarcoma

- third most common extracranial solid tumour of children (after neuroblastoma and Wilms' tumour)
- no clear predisposing risk factors
- common sites of origin are structures of the head and neck, GU tract and extremities
- presentation: firm, painless mass
- metastases to lung, bone marrow and bones
- evaluation: MRI or CT scan of primary site, CT chest, bone scan, bilateral bone marrow aspirates and biopsies
- treatment: multidrug chemotherapy and surgery

Lymphadenopathy

- features of malignant lymphadenopathy (LAD): firm, discrete, non-tender, enlarging, no associated erythema, warmth, fluctuance, \pm suspicious mass/imaging findings, \pm 'B' symptoms

Differential Diagnosis

- infection:
 - viral – URTI, EBV, CMV, adenovirus, HIV
 - bacterial – *S. aureus*, GAS, anaerobes, *Mycobacterium*, cat scratch disease (*Bartonella*)
 - other: fungal, protozoan, rickettsia
- auto-immune: rheumatoid arthritis, SLE, serum sickness
- malignancy: lymphoma, leukemia, metastatic solid tumours
- storage diseases: Niemann-Pick, Gauchers
- other: sarcoidosis, Kawasaki disease, histiocytoses

Investigations

- generalized LAD
 - CBC and differential, blood culture
 - uric acid, LDH
 - ANA, RF, ESR
 - EBV/CMV/HIV serology
 - toxoplasma titre
 - fungal serology
 - CXR
 - PPD
 - biopsy
- regional LAD
 - period of observation in an asymptomatic child
 - trial of oral antibiotics
 - biopsy (especially if persistent >6 weeks and/or 'B' symptoms)



Most common cause of acute bilateral cervical LAD is viral illness.

Respirology

Approach to Dyspnea

- see Table 1, *Average Vitals at Various Ages*, P3

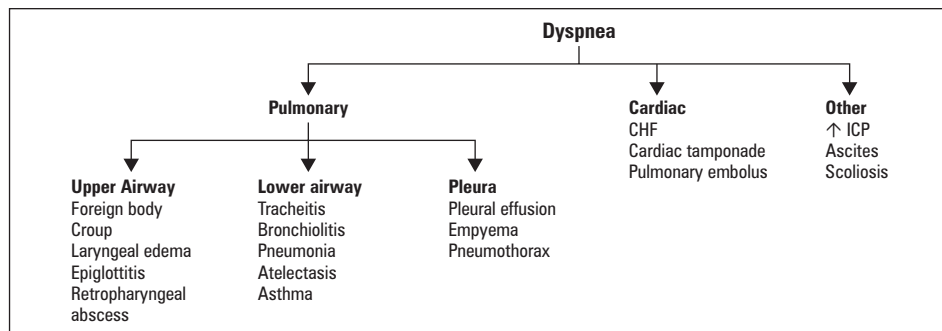


Figure 9. Approach to Dyspnea in Childhood

Upper Respiratory Tract Diseases

- see Otolaryngology, OT44
- disease above the thoracic inlet characterized by inspiratory stridor, hoarseness, and suprasternal retractions
- differential diagnosis of stridor
 - croup
 - bacterial tracheitis
 - epiglottitis
 - foreign body aspiration
 - subglottic stenosis: congenital or iatrogenic
 - laryngomalacia/tracheomalacia: collapse of epiglottis cartilage on inspiration

Table 47. Common Upper Respiratory Tract Infections

	Croup (Laryngotracheobronchitis)	Bacterial Tracheitis	Epiglottitis
Anatomy	Subglottic laryngitis	Subglottic tracheitis	Supraglottic laryngitis
Epidemiology	Common 6 mos-4 yrs Peak incidence: fall and early winter	Rare All age groups	Rare Usually older (2-6 yrs)
Etiology	Parainfluenza (75%) Influenza A and B RSV Adenovirus	<i>S. aureus</i> <i>H. influenzae</i> alpha-hemolytic strep Pneumococcus Moraxella catarrhalis	<i>H. influenzae</i> beta-hemolytic strep
Clinical Presentation	Hoarse voice Barking cough Stridor Worse at night	Similar symptoms as croup but more rapid deterioration with high fever Toxic appearance Does not respond to croup treatments	Toxic appearance Rapid progression Severe airway obstruction Drooling Stridor Tripod position Sternal recession Anxious
Investigations	Clinical diagnosis CXR in atypical presentation: "steep sign" from subglottic narrowing	Clinical diagnosis Endoscopy: definitive diagnosis	Clinical diagnosis Avoid examining the throat to prevent further respiratory exacerbation
Treatment	Humidified O ₂ Dexamethasone: PO 1 dose Racemic epinephrine: nebulized, 1-3 doses, q1-2 hours Intubation if unresponsive to treatment	Start therapy for croup Usually requires intubation Antibiotics	Intubation Antibiotics Prevented with Hib vaccine

Lower Respiratory Tract Diseases

- obstruction of airways below thoracic inlet, produces more expiratory sounds
- classic symptom: wheezing

Differential Diagnosis of Wheezing

- common
 - asthma: recurrent wheezing episodes, identifiable triggers
 - bronchiolitis: first episode of wheezing
 - recurrent aspiration: often neurological impairment
 - pneumonia: fever, cough, malaise
- uncommon
 - foreign body: acute wheezing and coughing
 - cystic fibrosis: prolonged wheezing, unresponsive to therapy
 - bronchopulmonary dysplasia: often develops after prolonged ventilation in the newborn
- rare
 - congestive heart failure
 - mediastinal mass
 - bronchiolitis obliterans
 - tracheobronchial anomalies

Pneumonia

- inflammation of pulmonary tissue, associated with consolidation of alveolar spaces

Clinical Presentation

- incidence is greatest in first year of life
- viral cause is more common in children <5 years old
- viral
 - cough, wheeze, stridor
 - CXR – diffuse, streaky infiltrates bilaterally
- bacterial
 - cough, fever, chills, dyspnea
 - CXR – lobar consolidation, possibly pleural effusion

Etiology and Management

- see Table 48
- supportive therapy: hydration, antipyretics, humidified O₂

Table 48. Common Causes and Treatment of Pneumonia at Different Ages

Age	Bacterial	Viral	Atypical Bacteria	Treatment
Neonates	GBS <i>E. coli</i> <i>Listeria</i>	CMV Herpes virus Enterovirus	<i>Mycoplasma hominis</i> <i>Ureaplasma urealyticum</i>	ampicillin + gentamicin / tobramycin (add erythromycin if suspect Chlamydia)
1-3 months	<i>S. aureus</i> <i>H. influenzae</i> <i>S. pneumoniae</i> <i>B. pertussis</i>	CMV, RSV Influenza virus Parainfluenza virus	<i>Chlamydia trachomatis</i> <i>Ureaplasma</i>	cefuroxime OR ampicillin ± erythromycin OR clarithromycin
3 months - 5 years	<i>S. pneumoniae</i> <i>S. aureus</i> <i>H. influenzae</i> GAS	RSV Adenovirus Influenza virus	<i>M. pneumoniae</i> , TB	ampicillin OR cefuroxime Mild: PO amoxicillin
>5 years	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>S. aureus</i>	Influenza virus Varicella Adenovirus	<i>Mycoplasma pneumoniae</i> (most common) <i>Chlamydia pneumoniae</i> TB <i>Legionella pneumophila</i>	erythromycin OR clarithromycin (1st line) OR ampicillin OR cefuroxime

Bronchiolitis

- defined as the first episode of wheezing associated with URTI and signs of respiratory distress

Epidemiology

- common, affects 50% of children in first 2 years of life
- peak incidence at 6 months, winter or early spring
- occurs in children prone to airway reactivity, increased incidence of asthma in later life

Etiology

- respiratory syncytial virus (RSV) (>50%)
- parainfluenza, influenza, rhinovirus, adenovirus, rarely *M. pneumoniae*

Clinical Presentation

- prodrome of URTI with cough and fever
- feeding difficulties, irritability
- wheezing, respiratory distress, tachypnea, tachycardia, retractions, poor air entry lasting for 5-6 days
- children with chronic lung disease, severe CHD and immunodeficiency have a more severe course of the illness

Investigations

- CXR (only needed in severe disease, poor response to therapy, chronic episode)
 - air trapping, peribronchial thickening, atelectasis, increased linear markings
- nasopharyngeal swab
 - direct detection of viral antigen (immunofluorescence)
- WBC usually normal

Treatment

- mild distress
 - supportive: oral or IV hydration, antipyretics for fever
 - humidified O₂ (maintain O₂ sat >92%)
 - inhaled bronchodilator (Ventolin®) 0.03 cc in 3 ml NS by mask, q20 min, and then hourly; stop if no response
- moderate to severe distress
 - as above – rarely, intubation and ventilation
 - ipratropium (Atrovent®) and steroids are not effective
 - consider rebetol (Ribavirin®) in high risk groups: bronchopulmonary dysplasia, CHD, congenital lung disease, immunodeficient
- monthly RSV-Ig or palivizumab (monoclonal antibody against the F-glycoprotein of RSV) may offer some protection against severe disease in high risk groups
 - case fatality rate <1%
- antibiotics have no therapeutic value unless there is secondary bacterial pneumonia
- indications for hospitalization
 - hypoxia: O₂ saturation <92% on initial presentation
 - persistent resting tachypnea >60/minute and retractions after several salbutamol (Ventolin®) masks
 - past history of chronic lung disease, hemodynamically significant cardiac disease, neuromuscular problem, immunocompromised
 - young infants <6 months old (unless extremely mild)
 - significant feeding problems
 - social problem (e.g. inadequate care at home)

Asthma

- see [Respirology](#), R7
- characterized by airway hyperreactivity, bronchospasm and inflammation, reversible small airway obstruction
- very common, presents most often in early childhood
- associated with other atopic diseases such as allergic rhinitis or atopic dermatitis

Clinical Presentation

- episodic bouts of
 - wheezing
 - dyspnea
 - cough: at night, early morning, with activity, with cold exposure
 - tachypnea
 - tachycardia
 - post-tussive emesis
- physical exam may reveal hyper-resonant chest, prolonged expiration, wheeze

Triggers

- URI (viral or *Mycoplasma*)
- weather (cold exposure, humidity changes)
- allergens (pets), irritants (cigarette smoke)
- exercise, emotional stress
- drugs (aspirin, beta-blockers)

Classification

- mild asthma
 - occasional attacks of wheezing or coughing (<2 per week)
 - symptoms respond quickly to inhaled bronchodilator
- moderate asthma
 - more frequent episodes with symptoms persisting and chronic cough
 - decreased exercise tolerance
- severe asthma
 - daily and nocturnal symptoms
 - frequent ER visits and hospitalizations

Management

- acute
 - O₂ to keep O₂ saturation >92%
 - fluids if dehydrated
 - beta2-agonists: salbutamol (Ventolin®) 0.03 cc/kg in 3 cc NS q20 minutes by mask until improvement, then masks hourly if necessary
 - ipratropium bromide (Atrovent®) if severe: 1 cc added to each of first 3 salbutamol masks
 - steroids: prednisone (2 mg/kg in ER, then 1 mg/kg daily x 4 days) or dexamethasone (0.3 mg/kg/day)
 - ♦ in severe disease, give steroids immediately since onset of action is slow (4 hours)
- indications for hospitalization
 - pre-treatment O₂ saturation <92%
 - past history of life-threatening asthma (ICU admission)
 - unable to stabilize with q4h masks
 - concern over environmental issues or family's ability to cope
- chronic
 - education, emotional support, avoid allergens or irritants, develop an "action plan"
 - exercise program (e.g. swimming)
 - monitoring of respiratory function with peak flow meter (improves adherence and allows modification of medication)
 - PFTs for children >6 years
 - patients with moderate or severe asthma will need regular prophylaxis in addition to bronchodilators (e.g. daily inhaled steroids, long-acting beta-agonists, anticholinergics, sodium cromoglycate, theophylline, leukotriene receptor antagonist)
- Canadian Paediatric Asthma Consensus Guidelines for assessing adequate control of asthma:
 1. daytime symptoms <4 days/wk
 2. night time symptoms <1 night/wk
 3. normal physical activity
 4. no work/school absenteeism
 5. need for beta agonist <4 doses/wk

Anti-Leukotriene Agents Compared to Inhaled Corticosteroids in the Management of Recurrent and/or Chronic Asthma in Adults and Children
Cochrane Database of Systematic Reviews 2004; Issue 1

27 randomized trials comparing anti-leukotrienes to inhaled corticosteroids in patients 2 years of age and older during a minimal 30-day intervention period.

Main Outcome: Rate of exacerbations requiring systemic corticosteroids.

Results: Patients receiving anti-leukotrienes were more likely to suffer an exacerbation requiring systemic steroids (RR 1.65, 95% CI 1.36 – 2.00). Only 3 trials focused on children and adolescents and the data could not be pooled.

Conclusions: For persistent asthma, inhaled glucocorticoids should remain the first line monotherapy; however more research is needed to determine its efficacy in children.

**CF Presenting Signs****CF PANCREAS**

Chronic cough and wheezing

Failure to thrive

Pancreatic insufficiency (symptoms of malabsorption like steatorrhea)

Alkalosis and hypotonic dehydration

Neonatal intestinal obstruction (meconium ileus)/Nasal polyps

Clubbing of fingers/Chest radiograph with characteristic changes

Rectal prolapse

Electrolyte elevation in sweat, salty skin

Absence or congenital atresia of vas deferens

Sputum with Staph or Pseudomonas (mucoid)

- Pancreatic dysfunction – determined by 3-day fecal fat collection
- Genetics – useful where sweat chloride test is equivocal

Cystic Fibrosis (CF)

- see [Respirology](#), R11
- autosomal recessive, CFTR gene found on chromosome 7 ($\Delta F508$ mutation in 70%, over 800 different mutations identified)
- 1 in 3,000 live births, mostly Caucasians
- mutation in transmembrane conductance regulator of chloride – causes cells to be impermeable to Cl which increases the reabsorption of Na
- leads to relative dehydration of airway secretions, resulting in impaired mucociliary transport and airway obstruction

Clinical Presentation

- neonatal
 - meconium ileus
 - prolonged jaundice
 - antenatal bowel perforation
- infancy
 - pancreatic insufficiency with steatorrhea and failure to thrive (despite voracious appetite)
- childhood
 - anemia, hypoproteinemia, hyponatremia
 - heat intolerance
 - wheezing or chronic cough
 - recurrent chest infections (*S. aureus*, *P. aeruginosa*, *H. influenzae*)
 - hemoptysis
 - nasal polyps (associated with milder disease)
 - distal intestinal obstruction syndrome, rectal prolapse
 - clubbing of fingers
- older patients
 - chronic obstructive pulmonary disease (COPD)
 - infertility

Investigations

- sweat chloride test x 2 (>60 mEq/L)
 - false positive tests: malnutrition, celiac disease, adrenal insufficiency, anorexia nervosa, hypothyroidism, nephrogenic diabetes insipidus, nephrotic syndrome
 - false negative tests: peripheral edema, cloxacillin, glycogen storage disease, hypoparathyroidism, atopic dermatitis, Klinefelter syndrome, hypogammaglobulinemia

Treatment

- nutritional counselling
 - high calorie diet
 - pancreatic enzyme replacements
 - fat soluble vitamin supplements
- management of chest disease
 - physiotherapy, postural drainage
 - exercise
 - bronchodilators
 - aerosolized DNAase
 - antibiotics: depends on sputum C&S (e.g. cephalosporin, cloxacillin, ciprofloxacin, inhaled tobramycin)
 - lung transplantation
- genetic counselling

Complications

- respiratory failure
- pneumothorax (poor prognostic sign)
- cor pulmonale (late)
- pancreatic fibrosis with diabetes mellitus
- gallstones
- cirrhosis with portal hypertension
- infertility
- early death (current median survival is 30 years)

Rheumatology



Evaluation of Limb Pain

Table 49. Differential Diagnosis of Limb Pain

Cause	<3 years	3-10 years	>10 years
Trauma	x	x	x
Infectious			
Septic arthritis	x	x	x
Osteomyelitis	x	x	x
Inflammatory			
Transient synovitis	x	x	
JIA	x	x	x
Seronegative spondyloarthropathy			x
SLE			x
Dermatomyositis			x
HSP		x	
Anatomic/Orthopaedic			
Legg-Calve-Perthes disease		x	x
Slipped capital femoral epiphysis			x
Osgood-Schlatter disease			x
Neoplastic			
Leukemia	x	x	x
Neuroblastoma	x	x	x
Bone tumour		x	x
Hematologic			
Hemophilia (hemarthrosis)	x	x	x
Sickle cell anemia	x	x	x
Pain Syndromes			
Growing pains		x	x
Fibromyalgia			x
Reflex sympathetic dystrophy			x

Investigations

- CBC, differential, blood smear, ESR
- x-rays of painful joints/limbs
- as indicated: blood C&S, ANA, RF, PTT, sickle cell prep, viral serology, immunoglobulins, complement, urinalysis, synovial analysis and culture, TB test, ASOT, slit lamp

Septic Arthritis

- medical emergency
- hematogenous osteomyelitic spread seen most commonly in neonates and infants
- clinical presentation: acute monoarthritis with erythema, warmth, swelling, intense pain on passive movement (pain may be so severe that it causes pseudoparalysis of involved limb), fever and chills
- definitive test: joint aspirate and culture
- management: proper antibiotic selection requires knowledge of likely bacterial pathogen at various ages

Table 50. Microorganisms Involved in Septic Arthritis/Osteomyelitis

Age	Pathogens	Treatment
Neonate	GBS, <i>S. aureus</i> , GNB	cloxacillin + aminoglycoside or cefotaxime
Infant (1-3 months)	<i>Strep. sp.</i> , <i>Staph. sp.</i> , <i>H. influenzae</i> Pathogens as per neonate	cloxacillin + cefotaxime
Child	<i>S. aureus</i> , <i>S. pneumoniae</i> , GAS	cefazolin
Adolescent	As above; also <i>N. gonorrhoeae</i>	cefazolin
Sickle cell disease	As above; also <i>Salmonella</i>	cefotaxime

GBS = group B Streptococcus; GNB = Gram-negative bacilli; GAS = group A Streptococcus
Adapted from Tse SML, Laxer RM. *Pediatrics in Review* 2006; 27:170-179.

Growing Pains

- age 2-12 years, M=F
- diagnosis
 - intermittent, well between episodes
 - poorly localized pain in the legs
 - usually bilateral
 - occurs in evening or awakens child at night
 - responds to reassurance, massage or analgesics
 - resolves completely in the morning
- no associated systemic symptoms (e.g. fever)
- possible family history of growing pains
- normal physical examination
- lab investigations not necessary if typical presentation

Transient Synovitis

- age 3-10 years, M>F
- benign, self limited disorder, usually occurs after upper respiratory tract infection, pharyngitis, bronchitis, otitis media

Clinical Presentation

- afebrile or low-grade fever, pain typically occurs in hips, knees, painful limp but still capable of ambulating
- symptoms resolve over 7-10 days

Investigations

- ESR, WBC within normal limits
- x-ray is typically normal
- U/S may show joint effusion
- must exclude septic arthritis, osteomyelitis, AVN, slipped capital femoral epiphysis (SCFE)

Treatment

- symptomatic and anti-inflammatory medications

Juvenile Idiopathic Arthritis (JIA)

- formerly known as Juvenile Rheumatoid Arthritis (JRA)
- a heterogeneous group of conditions characterized by persistent arthritis in children under 16 years
- diagnosis
 - arthritis in ≥ 1 joint(s)
 - duration ≥ 6 weeks
 - onset age < 16 years old
 - with exclusion of other causes of arthritis
- classification defined by features/number of joints affected in the first 6 months of onset

Systemic Arthritis (Still's disease)

- high spiking fever (38.5°C) for at least 2 weeks
- extra-articular features: erythematous "salmon-coloured" maculopapular rash, lymphadenopathy, hepatosplenomegaly, leukocytosis, thrombocytosis, anemia, serositis (pericarditis, pleuritis)
- onset at any age, M=F
- arthritis may occur weeks to months later
- high ESR, CRP, WBC, platelet count

Oligoarticular Arthritis (arthritis of 1-4 joints)

- persistent – affects no more than 4 joints during the disease course
- extended – affects more than 4 joints after the first six months
- onset 1-3 years of age, F > M
- typically affects large joints – knees > ankles, elbows, wrists, hip involvement unusual
- ANA positive ~80%, rheumatoid factor (RF) negative
- screening eye exams for asymptomatic anterior uveitis (occurs in ~20%)
- complications: knee flexion contracture, quadriceps atrophy, leg-length discrepancy, growth disturbances

Polyarticular Arthritis (arthritis of 5 or more joints)

- RF negative
 - often involves large and small joints of hands and feet, temporomandibular joint, cervical spine
 - patients, especially those who are ANA positive, are prone to chronic uveitis
- RF positive
 - similar to the aggressive form of adult rheumatoid arthritis
 - severe, rapidly destructive, symmetrical arthritis of large and small joints
 - may have rheumatoid nodules at pressure points (elbows, knees)
 - unremitting disease, persists into adulthood

Enthesitis-Related Arthritis

- arthritis and/or enthesitis with at least two of:
 - sacroiliac tenderness and/or inflammatory spinal pain
 - HLA B27 positive
 - family history of confirmed HLA B27-associated disease in a 1st or 2nd degree relative
 - symptomatic (acute) anterior uveitis
 - onset of arthritis in a boy >8 years

Psoriatic Arthritis

- arthritis and psoriasis or arthritis, and at least two of:
 - dactylitis, nail abnormalities, or family history of psoriasis in a 1st degree relative

Unclassified

- arthritis of unknown cause that persists for 6 weeks and either does not fulfill criteria for any category or fulfills criteria for more than one category

Management

- children may complain very little about their pain and disability
- exercise to maintain range of motion (ROM) and muscle strength
- multidisciplinary approach with OT/PT, social work, orthopedics, ophthalmology, rheumatology
- first line drug therapy: NSAIDs, intra-articular corticosteroids
- 2nd line
 - DMARDs – methotrexate, sulfasalazine
 - corticosteroids – systemic for systemic onset of JIA, topical eye drops for uveitis
 - biologic agents – etanercept (Enbrel®): binds TNF and blocks its interaction with cell surface receptors

Systemic Lupus Erythematosus (SLE)

- see [Rheumatology](#), RH9
- autoimmune illness affecting multiple organ systems
- incidence 1:1000; more commonly age >10, F:M = 10:1

Reactive Arthritis

- see [Rheumatology](#), RH22
- arthritis follows bacterial infection especially with *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Chlamydia*, and *Streptococcus* (post-streptococcal reactive arthritis)
- prognosis:
 - typically resolves
 - may progress to chronic illness or Reiter's syndrome (urethritis, conjunctivitis)

Lyme Arthritis

- see [Infectious Diseases](#), ID27
- caused by spirochete *Borrelia burgdorferi*
- incidence highest among 5-10 year olds
- arthritis begins months after initial infection (late Lyme disease)
- typically involves large joints, especially knees (affected in >90 % of cases)
- large, expanding erythematous macule with fever = erythema migrans of Lyme arthritis
- management: doxycycline or amoxicillin for 30 days; do not treat children <8 years old with doxycycline as it may cause permanent discolouration of teeth

Vasculitides

HENOCCH-SCHÖNLEIN PURPURA (HSP)

- most common vasculitis of childhood
- vasculitis of small vessels
- peak incidence 4-10 years, M:F = 2:1
- recurrence in about one third of patients
- often have history of URTI 1-3 weeks before onset of symptoms

Clinical Presentation

- skin: palpable, non-thrombocytopenic purpura in lower extremities and buttocks, edema, scrotal swelling
- joints: arthritis/arthralgia involving large joints
- GI: abdominal pain, GI bleeding, intussusception
- renal: IgA nephropathy, hematuria, proteinuria, hypertension, renal failure in <5%

Management

- symptomatic, corticosteroids may relieve abdominal pain
- monitor for renal disease, may develop late
- immunosuppressive therapy for severe renal disease

Prognosis

- self-limited disease in 90%

Kawasaki Disease

- acute vasculitis of unknown etiology
- mainly affecting medium-size arteries
- most common cause of acquired heart disease in children
- peak age <5 years; East Asians > Blacks > Caucasians

Diagnostic Criteria

- fever persisting 5 days or more AND
- 4 of the following features:
 1. bilateral nonpurulent conjunctivitis
 2. red fissured lips, strawberry tongue, erythema of oropharynx
 3. changes of the peripheral extremities
 - ♦ acute phase: erythema, edema of hands and feet
 - ♦ subacute phase: peeling from tips of fingers and toes
 4. polymorphous rash
 5. cervical lymphadenopathy >1.5 cm in diameter
- exclusion of other diseases (e.g. scarlet fever, measles)
- atypical Kawasaki disease: less than 5 of 6 diagnostic features but coronary artery involvement

Associated Features

- acute phase (as long as fever persists, about 10 days)
 - most of diagnostic criteria present
 - irritability, aseptic meningitis, myocarditis, pericarditis, CHF
 - diarrhea, gallbladder hydrops, pancreatitis, urethritis, arthritis
- subacute phase (resolution of fever, peeling of skin, elevated ESR and platelets, usually days 11-21)
 - arthritis
 - beau's lines seen on nail growth
- convalescent phase (lasts until ESR and platelets normalize, >21 days)
 - coronary artery aneurysms, aneurysm rupture, myocardial infarction (MI), CHF

Management

- high (anti-inflammatory) dose of ASA while febrile
- low (anti-platelet) dose of ASA in subacute phase until platelets normalize or longer if coronary artery involvement
- IV immunoglobulin (2 g/kg) reduces risk of coronary aneurysm formation
- baseline 2D-echo and follow up periodic 2D-echocardiograms (usually at 6 weeks)

Complications

- coronary artery vasculitis with aneurysm formation occurs in 20-25% of untreated children, <5% if receive IVIG within 10 days of fever
 - 50% of aneurysms regress within 2 years
 - anticoagulation for multiple or large coronary aneurysms
- risk factors for coronary disease: male, age <1 or >9 years, fever >10 days



Diagnostic Criteria for Kawasaki Disease

Warm **CREAM**

Fever ≥5 days

Conjunctivitis

Rash

Edema/Erythema (hands and feet)

Adenopathy

Mucosal involvement

Common Medications

Table 51. Commonly Used Medications in Pediatrics

Drug Name	Dosing Schedule	Indications	Comments
acetaminophen (Tylenol®)	10-15 mg/kg/dose PO/PR q4-6h prn	Analgesic, antipyretic	
amoxicillin (Amoxil®)	80-90 mg/kg/day PO divided q8h	Otitis media	
dexamethasone	0.6 mg/kg IV x 1 OR 1 mg/kg PO x 1 0.3 mg/kg/day PO	Croup Acute asthma	
fluticasone (Flovent®)	moderate dose – 250-500 µg/day divided bid high dose – >500 µg/day divided bid	Asthma	
ibuprofen (Advil®)	5-10 mg/kg/dose PO q6-8h	Analgesic, antipyretic	Cautious use in patients with liver impairment, history of GI bleeding or ulcers
iron	6 mg/kg/day elemental iron bid-tid	Anemia	Side effects: dark stool, constipation, dark urine
prednisone	1-2 mg/kg/day PO x 5 days 3-4 mg/kg/day PO 60 mg/m ² /day PO	Asthma ITP Nephrotic syndrome	
salbutamol (Ventolin®)	0.01-0.03 mL/kg/dose in 3 mL normal saline via nebulizer q1/2-4h prn 100-200 µg/dose prn, max frequency q4h	Acute asthma Maintenance treatment for asthma	

From Lau, E. (2009) *The 2009-2010 Formulary – The Hospital for Sick Children*

References

Cardiology

- Anita Bhandari and Vineet Bhandari. Pitfalls, Problems, and Progress in Bronchopulmonary Dysplasia. *Pediatrics* 2009; 123: 1562-1573.
- Smythe J. Does every childhood heart murmur need an echocardiogram? *The Canadian Journal of Pediatrics*. Volume 2 – Number 4.
- Task Force on Blood Pressure Control in Children: Report of the Second Task Force on Blood Pressure Control in Children – 1987. Task Force on Blood Pressure Control in Children. National Heart, Lung, and Blood Institute, Bethesda, Maryland. *Pediatrics*. 1987 Jan; 79(1):1-25.

Endocrinology

- American Diabetes Association. Type 2 Diabetes in Children and Adolescents. *Pediatrics*. 2000; 105(3): 671-681.
- Lenhard MJ, Reeves GD. Continuous subcutaneous insulin infusion: a comprehensive review of insulin pump therapy. *Archives of Internal Medicine*. 2001;161(19):2293-3000.
- Muir, A., et al. Precocious Puberty. *Pediatrics in Review*. 2006;27(10): 373-380.
- Styne DM, Glaser NS. Endocrinology. *Nelson's Essentials of Pediatrics*. 4th Edition. W.B. Saunders co. pp 711-766, 2002.

Gastroenterology

- Kirshner BS, Black DD. The Gastrointestinal Tract. In *Nelson's Essentials of Pediatrics*. 3rd Edition. pp. 419-458, 1998.
- Nutrition for Healthy Infants – Statement of the Joint Working Group: Canadian Pediatric Society, Dieticians of Canada, Health Canada.
- Scott, RB. Recurrent abdominal pain during childhood. *Canadian Family Physician*. 1994;40:539-547.

General Topics

- 2009-2010 Drug Handbook and Formulary. In: Lau E, ed. Toronto: The Hospital for Sick Children Department of Pharmacy; 2009.
- Albright EK. Current Clinical Strategies. Pediatric History and Physical Examination. 4th Edition. Current Clinical Strategies Publishing 2003.
- Apparent Life-Threatening Events. *Pediatric Emergency Medicine*. Saunders Elsevier. pp269-272, 2008.
- D'Augustine S, Fiosi T. *Tarascon Pediatric Outpatient Pocketbook*. 1st Ed. Tarascon Publishing; 2008.
- Greer FR, et al. Effects of nutritional interventions on the development of atopic disease in infants and children: The role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics*. 2008;129:183-191
- McGahren ED, Wilson WG. *Pediatrics Recall*. 3rd ed. Baltimore: Lippincott Williams & Wilkins; 2008.
- Nelson essentials of pediatrics*. 5th ed. Philadelphia, PA.: Elsevier Saunders; 2006.
- Objectives for the Qualifying Examination. Medical Council of Canada. Third Edition, 2004.
- Scruggs K, Johnson MT. *Pediatrics 5-minute reviews*. Current Clinical Strategies Publishing. 2001-2002.
- Shields, Margot. Measured obesity: Overweight Canadian children and adolescents. Nutrition findings from the Canadian Community Health Survey. Statistics Canada. 2005.
- The Hospital for Sick Children Handbook of Pediatrics. In: Dipchand A, Friedman J, Bismilla Z, Gupta S, Lam C, eds. 11th ed. Toronto: Elsevier Canada; 2009.
- The Hospital for Sick Children Handbook of Pediatric Emergency Medicine. Sudbury, Mass.: Jones and Bartlett Publishers; 2008.

Genetic Disorders and Developmental Disorders

- Amato RSS. Human Genetics and Dysmorphology. *Nelson's Essentials of Pediatrics*. 3rd Edition. W.B. Saunders co. pp 129-146, 2002.
- Blake KD, Prasad C. CHARGE Syndrome. *Orphanet Journal of Rare Diseases*. 2006;1:34
- Biggar W. Duchenne Muscular Dystrophy. *Pediatrics in Review*. 2006;27(3):83-88.
- Chudley AE, Conry J, Cook JL, Loock C, Rosales T, LeBlanc N; Public Health Agency of Canada's National Advisory Committee on Fetal Alcohol Spectrum Disorder. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. *CMAJ*. 2005;172(5 Suppl):S1-S21.
- Nicholson JF. Inborn errors of metabolism. *Nelson's Essentials of Pediatrics*. 4th Edition. W.B. Saunders co. pp 153-178, 2002.
- Vissers LE, et al. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nature Genetics*. 2004;36(9):955-957

Hematology

- Corrigan J, Boineau F. Hemolytic-Uremic Syndrome. *Pediatrics in Review*. 2001 Nov; 22(11).
- Pearce JM, Sills RH. Childhood Leukemia. *Pediatrics in Review*. 2005; 26(3):96-102.
- Segel GB. Anemia. *Pediatrics in Review*. 1988 Sep; 10(3).
- Silverstein J. et al. Care of Children and Adolescents with Type 1 Diabetes: A Statement of the American Diabetes Association. *Diabetes Care*. 2005; 28(1):186-208.

Infectious Disease and Immunizations

- Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatric Infectious Disease Journal*. 2000;19(3):187-195.
- Canada Communicable Disease Report. Statement on recommended use of varicella virus vaccine. An Advisory Committee Statement (ACS) National Advisory Committee on Immunization. 1999; Volume 25. ACS-1.
- Canada Communicable Disease Report. Statement on recommended use of meningococcal vaccines. An Advisory Committee Statement National Advisory Committee on Immunization. 2001; Volume 27. ACS-6.
- Canada Communicable Disease Report. Statement on recommended use of pneumococcal conjugate vaccine. An Advisory Centers for Disease Control and Prevention. Managing acute gastroenteritis among children. 2003; 52 (No.RR-16).
- Advisory Committee Statement National Advisory Committee on Immunization. Volume 28. ACS-2.
- National Advisory Committee on Immunization. Recommended Immunization Schedule for Infants, Children, and Youth (updated March 2005). Canadian Immunization Guide – 6th Edition.
- Publicly Funded Immunization Schedules for Ontario – January 2009.
- Treatment of acute otitis media in an era of increasing microbial resistance. *Pediatric Infectious Diseases Journal*. 1998; 17:576-579.
- Wubbel L, McCracken D, McCracken GH. Management of Bacterial Meningitis. *Pediatrics in Review*. 1998 Mar; 19(3).

Neonatology

- Gomella TL, Cunningham MD, Eyal FG, Zenk KE. Assessment of gestational age. *Neonatology: Management, Procedures, On-call Problems, Diseases and Drugs*. 5th edition. McGraw-Hill Companies. pp 21-28, 491-6, 559-62, 2004.
- Jain L and Douglas E. Physiology of Fetal Lung Fluid Clearance and the Effect of Labor. *Seminars in Perinatology* 2006.
- Joseph J Zorc; Zlatka Kanic A cyanotic infant: True blue or otherwise? *Pediatric Annals*; Oct 2001; 30, 10; Research Library pg. 597
- Meinzen-Derr J, Poindexter B, Wrage L, Morrow AL, Stoll B, Donovan EF. Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. *J Perinatol* 2009;29(1):57-62.
- Niermeyer S. et al. International Guidelines for Neonatal Resuscitation: An excerpt from the Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: International Consensus on Science. Contributors and Reviews for the Neonatal Resuscitation. Guidelines. *Pediatrics*. 2000; 106(3):E29.

Nephrology

- Diven SC, Luther BT. A practical primary care approach to hematuria in children. *Pediatric Nephrology*. 2000; 14:65-72.
- Hogg RJ, Portman RJ, Milliner D, Lemley KV, Eddy A, Ingelfinger J. Evaluation and management of proteinuria and nephrotic syndrome in children: Recommendations from a pediatric nephrology panel established at the National Kidney Foundation Conference on proteinuria, albuminuria, risk, assessment, detection and elimination (PARADE). *Pediatrics*. June; 105(6):1242-1249.
- Michael RS. Toilet training. *Pediatrics in Review*. 1999; 20(7).

Neurology

- Bergman I, Painter MJ. Neurology. Nelson's Essentials of Pediatrics. 4th Edition. W.B. Saunders co. pp 767-820, 2002.
- Hirtz D, Ashwal S, Berg A, et al. Practice parameter: Evaluation a first nonfebrile seizure in children. Report of the quality standards subcommittee of the American Epilepsy Academy of Neurology. The Child Neurology Society and The American Epilepsy Society. *Neurology*. 2000 Sep 12; 55(5):616-23.
- Levy RG, Cooper PP. Ketogenic diet for epilepsy. *Cochrane Database of Systematic Reviews* 2003, Issue 3.
- Lewis DW, Ashawal S, Dahl G, et al. The Quality Standards Subcommittee of the American Academy of Neurology. The Practice Committee of the Child Neurology Society. Practice parameter: Evaluation of children and adolescents with recurrent headaches. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Guideline. *Neurology*. 2002 Aug 27; 59(4):490-498.
- Lewis, D et al. Practice Parameter: Pharmacological treatment of migraine headache in Children and adolescents. American Academy of Neurology. *Neurology*. 2004; 63:2215-2224.
- Tenenbaum S. Disseminated encephalomyelitis in Children. *Clinical Neurology and Neurosurgery*. November 2007. Elsevier.

Pharmacology

- Hospital for Sick Children. Formulary of Infant and Enteral Formulas. February 2006.
- Kowalczyk A (Ed.). The 2004-2005 Formulary – The Hospital for Sick Children. Toronto: The Graphic Centre, HSC.

Respirology

- Ducharme F, di Salvo F. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* 2004, Issue 1.
- Garrison MM, Christakis DA, Harvey E, Cummings P, Davis RL. Systemic corticosteroids in infant bronchiolitis: a meta-analysis. *Pediatrics*. 2000;105:e44.
- Jain, L and Dudell G. Respiratory Transition in Infants Delivered by Cesarean Section. *Seminars in Perinatology*. 2006 Elsevier

Rheumatology

- Olson JC. Rheumatic Diseases of Childhood. Nelson's Essentials of Pediatrics. Third Edition. W.B. Saunders co. pp299-314, 1998.
- Schneider R. Pinpointing the cause of limb pain in children. *Pediatrics*. 1993:576-583.

Web-based Resources

- <http://www.medscape.com/home/topics/pediatrics>
- <http://www.icndata.com/health/pedbase>
- <http://www.cda-adc.ca>
- <http://www.aboutkidshealth.ca>
- <http://www.healthychildren.org>
- <http://www.publichealth.gc.ca>

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Basic Anatomy Review

Skin

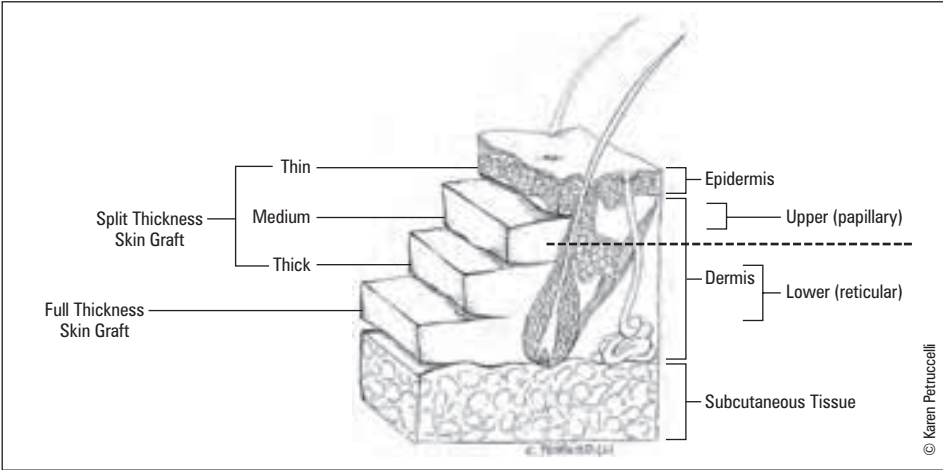


Figure 1. Split and Full (whole) Thickness Skin Grafts

Hand

BONES AND NERVES



Carpal Bone Mnemonic
(in order: proximal then distal row, radial to ulnar side)
Some – Scaphoid
Lovers – Lunate
Try – Triquetrum
Positions – Pisiform
That – Trapezium
They – Trapezoid
Cannot – Capitate
Handle – Hamate

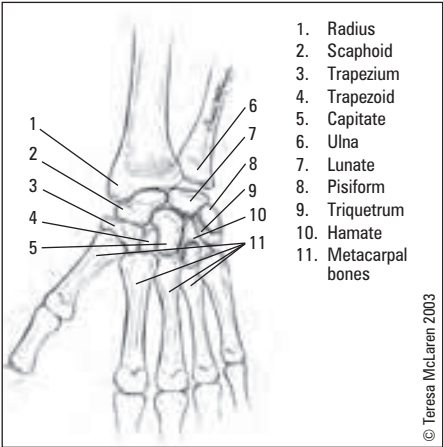


Figure 2. Carpal Bones

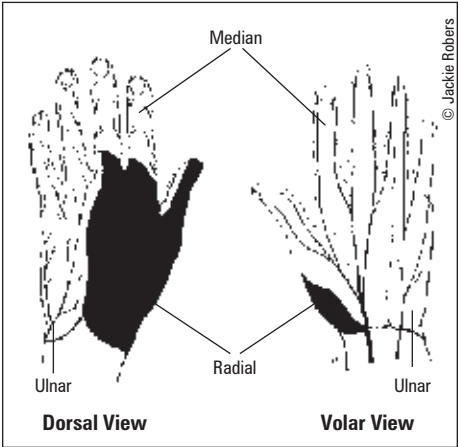


Figure 3. Sensory Distribution in the Hand

TENDONS

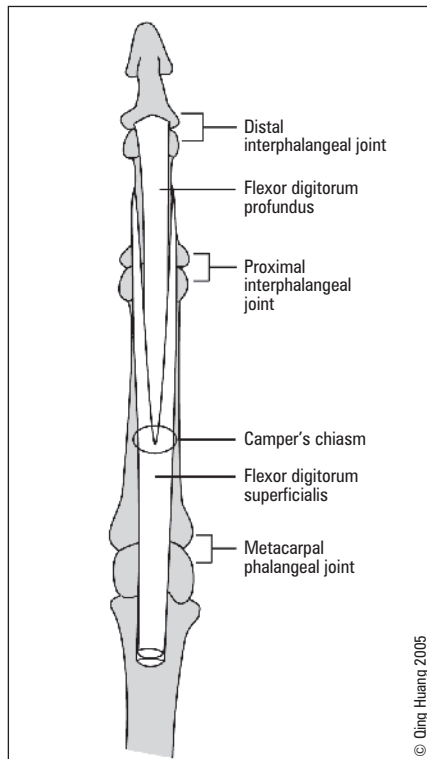


Figure 4. Flexor Tendon Insertion at PIP and DIP

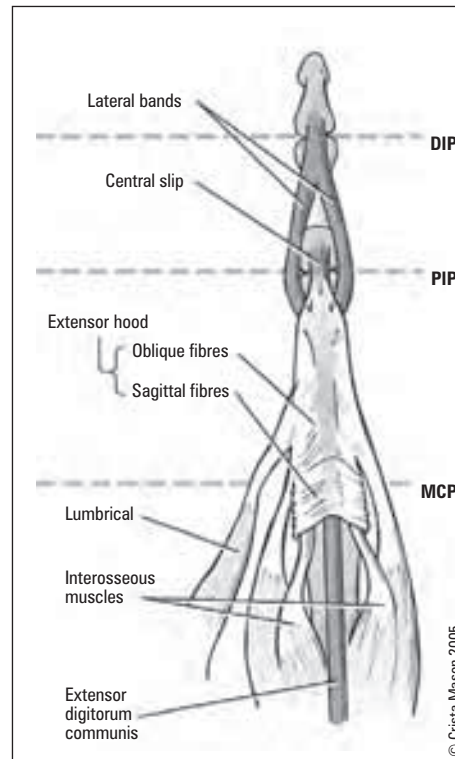


Figure 5. Extensor Mechanism of Digits

**Flexor Tendons**

All require OR repair.

Extensor Tendons

ER repair unless proximal/multiple tendons.

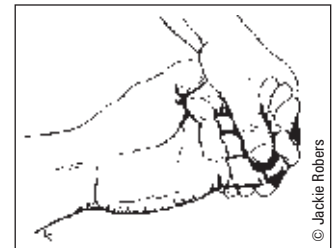


Figure 6. Testing Profundus (FDP)



Figure 7. Testing Superficialis (FDS)

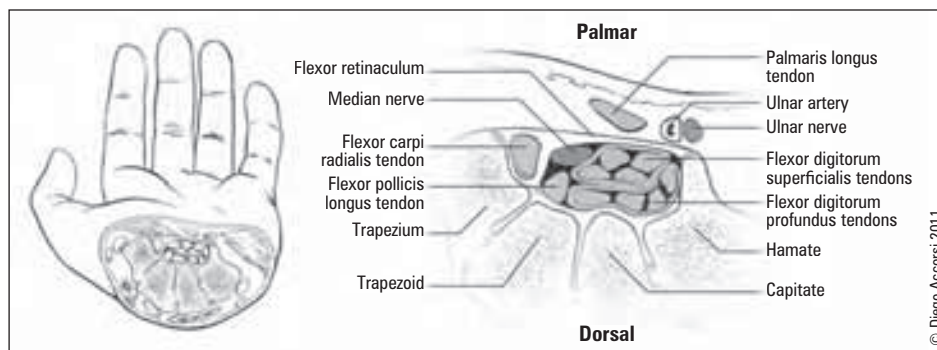


Figure 8. Carpal Tunnel

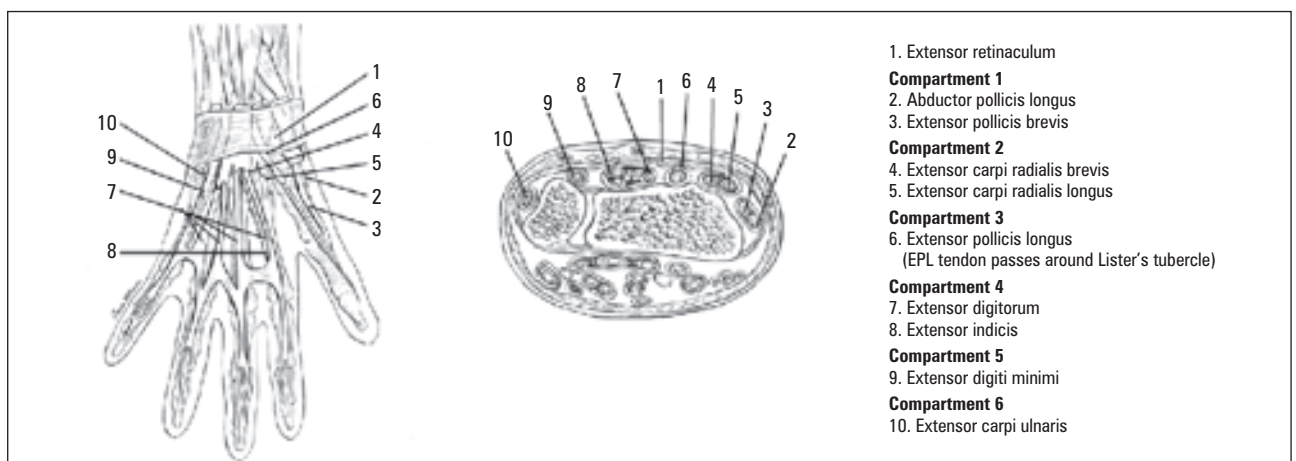


Figure 9. Extensor Compartments of the Wrist (dorsal view and cross-sectional view)

Brachial Plexus



Brachial Plexus Mnemonic
Rob – Roots
Thomas – Trunks
Drinks – Divisions
Cold – Cords
Beers – Branches

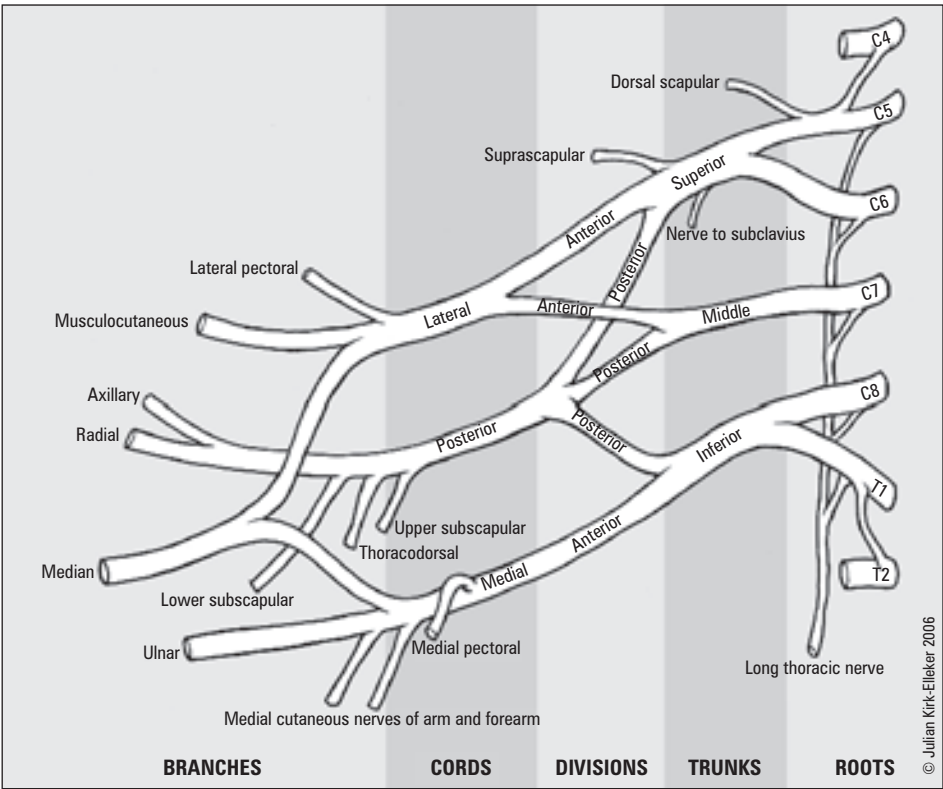


Figure 10. Brachial Plexus Anatomy

Face

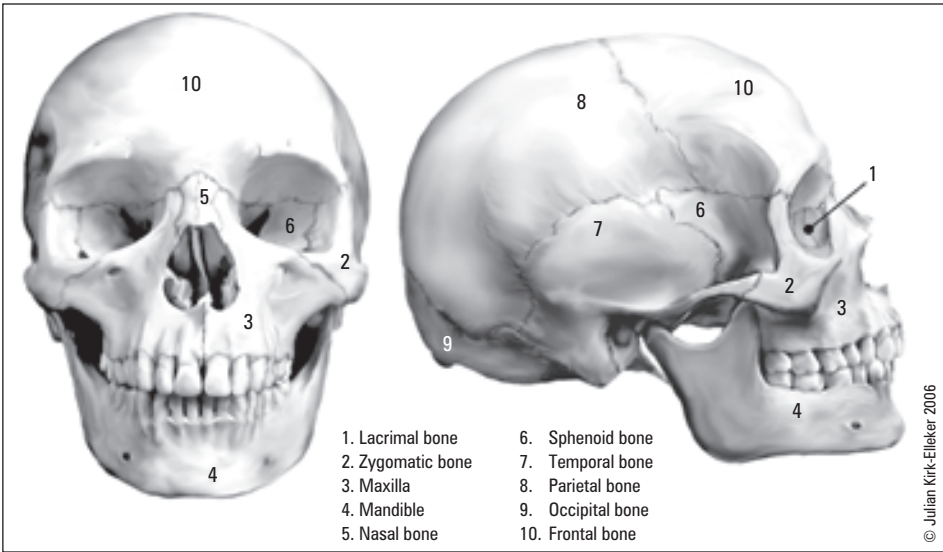


Figure 11. Skull and Facial Bones

Differential Diagnoses of Common Presentations

DDx of Skin Lesions/Masses

- For background information, see [Dermatology](#), D3

Basic Surgical Techniques

Sutures and Suturing

ANESTHESIA

- inject anesthetic before final debridement and irrigation
- lidocaine (Xylocaine®) ± epinephrine (vasoconstrictor, limits bleeding)
 - toxic limit and duration of action (1 cc of 1% solution contains 10 mg lidocaine):
 - without epinephrine: 5 mg/kg, lasts 46-60 min
 - with epinephrine: 7 mg/kg, lasts 2-6 hours
 - signs of toxicity: CNS excitation followed by CNS, respiratory, and cardiovascular depression
- bupivacaine (Marcaine®) ± epinephrine used for longer analgesic effect
 - toxic limit and duration of action:
 - without epinephrine: 2 mg/kg, lasts 2-4 hours
 - with epinephrine: 3 mg/kg, lasts 3-7 hours
- toxicity of mixtures (i.e. lidocaine + bupivacaine) is no greater than its individual components

IRRIGATION AND DEBRIDEMENT

- irrigate copiously with a physiologic solution such as Ringer's lactate or normal saline to remove surface clots, foreign material, and bacteria
- debride all obviously devitalized tissue, irregular or ragged wounds must be excised to produce sharp wound edges that will assist healing when approximated

SUTURES

- use of a particular suture material is highly dependent on surgeon preference
- suture material divided by two categories:
 - absorbable vs. non-absorbable:
 - absorbable materials commonly used for deep sutures under short-term tension
 - also used for skin closure in children or uncooperative adults
 - lose at least 50% of their strength in 4 weeks and are eventually absorbed
 - examples include Plain gut®, Vicryl®, Polysorb®
 - non-absorbable materials commonly used for skin closure or in sites of long term tension
 - lower likelihood of wound dehiscence
 - examples include nylon, polypropylene, stainless steel
 - monofilament vs. multifilament (a.k.a twisted or braided)
 - monofilament sutures slide through tissue with less friction but have more memory/stiffness
 - used in contaminated and infected wounds
 - lower likelihood of bacterial trapping in suture material
 - examples include Monosof®, Monocryl®, Biosyn®
 - multifilament sutures have less memory/stiffness making them easier to work with
 - increased likelihood of bacterial trapping, should be avoided in contaminated wounds
 - includes Vicryl® and Silk

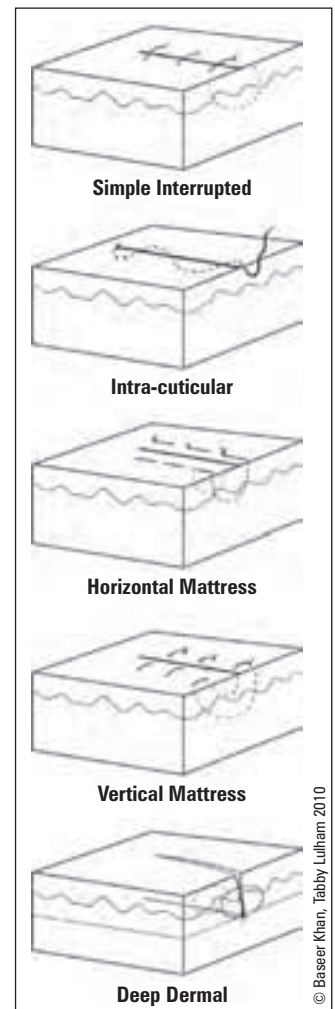


Figure 12. Basic Suture Methods

BASIC SUTURING TECHNIQUES

Basic Suture Methods (Figure 12)

- simple interrupted – can be used in almost all situations
- intra-cuticular – good cosmetic result but weak, used in combination with deep sutures
- vertical mattress – for areas difficult to evert (e.g. dorsum of the hand)
- horizontal mattress – everting, time saving
- continuous over and over (a.k.a “running”, “baseball stitch”) – time saving, good for hemostasis

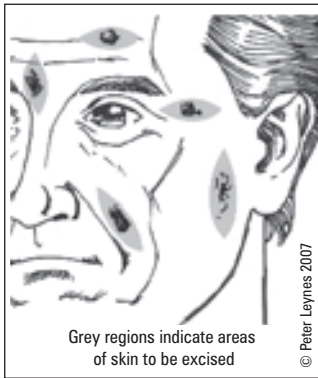


Figure 13. Incision of Lesions Along Relaxed Skin Tension Lines



Relaxed Skin Tension Lines

Natural skin/wrinkle lines with minimal linear tension. Placing incisions parallel to RSTLs minimizes widening/hypertrophy, and helps to camouflage scars.

Basic Principles

- minimize tissue trauma: follow curve of needle, handle wound edges gently (use toothed forceps), use just enough tension to approximate edges (do not strangulate)
- use the finest needle and suture possible
- to ensure good cosmesis
 - evert skin edges when closing
 - avoid tension on skin (close in layers)
 - ensure equal width and depth of tissue on both sides
 - remove sutures within 7-10 days (5 days for the face)

Other Skin Closure Materials

- tapes – may be indicated for superficial wounds and those with opposable edges. Tape cannot be used on actively bleeding wounds. When placed across the incision, will prevent surface marks and can be used primarily or after surface sutures have been removed. Tape burns may occur if there is excessive tension or swelling around the incision
- skin adhesives – e.g. 2-octylcyanoacrylate (e.g. Dermabond®) works well on small areas without much tension or shearing. Advisable in children. May cause tattooing
- staples – steel-titanium alloys that incite minimal tissue reaction (healing is comparable to wounds closed by suture)

Excision

- incise along relaxed skin tension lines (RSTLs) to minimize appearance of scar
- use elliptical incision to prevent “dog ears” (heaped up skin at end of incision)
- if needed, undermine skin edges to decrease wound tension
- use layered closure including dermal sutures when wound is deeper than superficial (decreases tension)

Wounds

Causal Conditions

- laceration – cut or torn tissue
- abrasion – superficial skin layer is removed, variable depth
- contusion – injury caused by forceful blow to the skin and soft tissue; entire outer layer of skin intact yet injured
- avulsion – tissue/limb forcefully separated from surrounding tissue, either partially or fully; “de-gloving”
- puncture wounds – opening relatively small as compared with depth (e.g. needle)
 - includes bite wounds
- crush injuries – caused by compression
- thermal and chemical wounds

Principles of Wound Healing

- wound: disruption of the normal anatomical relationships of tissue as a result of injury



STAGES OF WOUND HEALING

- see Figure 14
- growth factors released by tissues play an important role

FACTORS INFLUENCING WOUND HEALING

Local (reversible/controllable):

- mechanical (local trauma, tension)
- blood supply (ischemia/circulation)
- temperature
- technique and suture materials
- retained foreign body
- infection
- hematoma/seroma (↑ infection rate)
- venous hypertension
- peripheral vascular disease

General (often irreversible):

- age
- nutrition (protein, vit. C, O₂)
- smoking
- chronic illness (e.g. diabetes, cancer, CVD)
- immunosuppression (steroids, chemo, radiation)
- collagen vascular disease
- tissue irradiation



Myofibroblasts are the cells responsible for wound contraction. They do this at a rate of less than 0.75 mm/day.

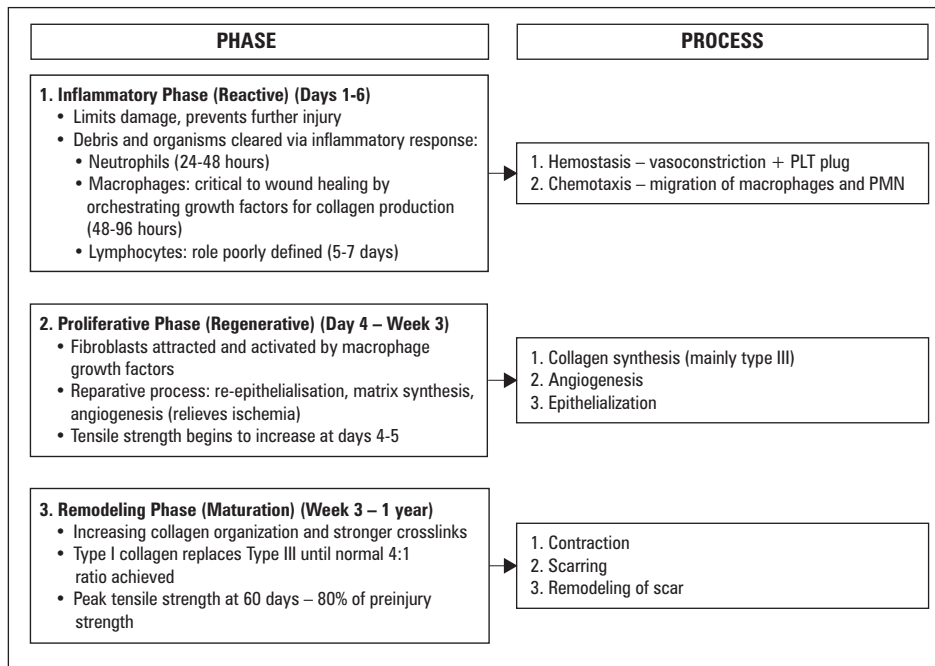


Figure 14. Stages of Wound Healing

ABNORMAL HEALING

Hypertrophic Scar

- scar remains roughly within boundaries of original injury
- red, raised, widened, frequently pruritic
- common sites: back, shoulder, sternum
- treatment: pressure garments, silicone gel sheeting, corticosteroid injection, surgical excision if other options fail (however, may still recur), typically improves with time

Keloid Scar

- scar extends beyond boundaries of original injury
- frequently pruritic, often painful; collagen in whorls rather than bundles
- common sites: sternum, deltoid, earlobe; more common in darker skinned people
- treatment: pressure garments, silicone gel sheeting, corticosteroid injection, radiation therapy, surgical excision as a last resort

Chronic Wound

- fails to heal primarily within 6 weeks
- common chronic wounds include diabetic, pressure and venous stasis ulcers
- treatment: may heal with meticulous wound care; many require surgical intervention
- Marjolin's ulcer: squamous cell carcinoma arising in a chronic wound secondary to genetic changes caused by chronic inflammation → consider biopsy of chronic wound

WOUND CLOSURE

Primary (1°) Closure (First Intention)

- definition: wound closure by direct approximation of edges within hours of wound creation (i.e. with sutures, staples, skin graft, etc.)
- indication: recent (<6 hours, longer with facial wounds), clean wounds
- contraindications: animal/human bites (except on face), crush injuries, infection, long time lapse since injury (>6-8 hours), retained foreign body

Secondary (2°) Closure/Spontaneous Healing (Second Intention)

- definition: wound left open to heal spontaneously (epithelialization 1 mm/day from wound margins in concentric pattern), contraction (myofibroblasts) and granulation – maintained in inflammatory phase until wound closed; requires dressing changes; inferior cosmetic result
- indication: when 1° closure not possible or indicated (see *Primary Closure*, above)

Tertiary (3°) Closure/Delayed Primary Closure (Third Intention)

- definition: intentionally interrupt healing process (e.g. with packing), then wound is usually closed at 4-10 days post-injury after granulation tissue has formed and there is $<10^5$ bacteria/gram of tissue
- indication: contaminated (high bacterial count), long time lapse since initial injury, severe crush component with significant tissue devitalization
- prolongation of inflammatory phase decreases bacterial count and lessens chance of infection after closure

Contaminated and Infected Wounds**Definitions**

- contamination – the presence of non-replicating microorganisms within a wound
- colonization – the presence of replicating microorganisms within a wound
- infection – greater than 10^5 microorganisms in a wound without intact epithelium, a wound may also be infected with small amounts of a very virulent organism (e.g. GBS)

Acute Contaminated Wound (<24 hr)

- cleanse and irrigate open wound with physiologic solution (NS or RL)
- debridement: removal of foreign material, devitalized tissue, old blood
 - surgical debridement: blade and irrigation if indicated
- evaluate for injury to underlying structures (vessels, nerve, tendon and bone)
- control active bleeding
- systemic antibiotics are commonly indicated for obvious infection, wound older than 8 hours, severely contaminated, immunocompromised, involvement of deeper structures (e.g. joints, fractures)
- \pm tetanus toxoid (Td) 0.5 ml IM \pm tetanus immunoglobulin 250 U deep IM (see Table 1 and Table 2)
- \pm postexposure treatment of
 - hepatitis B, HIV, (hepatitis C if titres confirmed at 6 months)
- re-evaluate in 24-48 hours for signs of deep infection
 - open infected portion of wound by removing sutures if evidence of infection (i.e. erythema, warmth, pain, discharge)



Infection is based on:

1. Virulence of the infecting microorganism
2. Amount of bacteria present
3. Host resistance

Table 1. Risks for Tetanus

Wound Characteristics	Tetanus-Prone	Not Tetanus-Prone
Time since injury	>6 h	<6 h
Depth of injury	>1 cm	<1 cm
Mechanism of Injury	Crush, burn, gunshot, frostbite, puncture through clothing, farming injury	Sharp cut (e.g. clean knife, clean glass)
Devitalized tissue	Present	Not present
Contamination (e.g. soil, dirt, saliva, grass)	Yes	No
Retained foreign body	Yes	No

Table 2. Tetanus Immunization Recommendations

History of tetanus immunization	Clean, minor wounds		All other wounds	
	Td or Tdap*	Tig**	Td or Tdap	Tig
Uncertain or <3 doses of immunization	Yes	No	Yes	Yes
3 doses received in immunization series	No~	No	No§	No¶

* 0.5 ml of combined tetanus and diphtheria toxoids \pm acellular pertussis.

** Tetanus immune globulin, 250 U given at a separate site from Td/Tdap

~ Yes, if > 10 years since last booster

§ Yes, if > 5 years since last booster.

¶ Yes, if immunocompromised.

Contaminated Wounds (>24 hours, including ulcers)

- irrigation and debridement
 - traumatic tattooing can occur if foreign materials left in wound
- topical antimicrobial – avoid inhibitors of epithelialization (see Table 3)
- systemic antibiotics indicated if there is concern of infection (eg. redness, swelling, pain, clinically unwell)
- closure: final closure via secondary intention (most common), delayed wound closure (3° closure), skin graft or flap; successful closure depends on bacterial count of $\leq 10^5$ prior to closure and frequent dressing changes

BITES

Dog and Cat Bites

- pathogens: *Pasteurella multocida*, *S. aureus*, *S. viridans*
- investigations: same as for human bites; see below
- treatment: Clavulin® (500 mg PO q8h started immediately – amoxicillin + clavulanic acid)
 - consider rabies prophylaxis if animal has symptoms of rabies or unknown animal
 - ♦ ± rabies Ig (20 IU/kg around wound, or IM) and 1 of the 3 types of rabies vaccines (1.0 ml IM in deltoid, repeat on days 3, 7, 14, 28)
 - aggressive irrigation with debridement
 - healing by second intention is mainstay of treatment (see Emergency Medicine, ER47)
 - only consider primary closure for bite wounds on the face; otherwise primary closure is contraindicated
 - contact Public Health if animal status unknown

Human Bites

- pathogens: Staph > α-hemolytic Strep > *Eikenella corrodens* > Bacteroides)
- mechanism: most commonly over dorsum of MCP from a punch in mouth; “fight-bite”
- serious, as mouth has 10⁹ microorganisms/mL, which get trapped in joint space when fist unclenches and overlying skin forms an air-tight covering ideal for anaerobic growth – can lead to septic arthritis
- investigations:
 - radiographs prior to therapy to rule out foreign body (tooth)/fracture
 - culture for aerobic and anaerobic organisms, Gram stain
- treatment:
 - **urgent surgical exploration** of joint, drainage and debridement of infected tissue
 - wound must be copiously irrigated
 - Clavulin® 500 mg PO q8h, clindamycin 300 mg PO q6h + ciprofloxacin 500 mg PO q12h (if allergic to penicillin) + secondary closure (see Emergency Medicine, ER47)
 - splint

Dressings

- there is no one dressing for any given type of wound. Dressing selection depends on the wound characteristics
 - as the wound progresses through healing it will require different types of dressings, therefore, routine inspection is recommended
 - principles of dressings:
 - ♦ wet vs. dry wounds
 - purpose of dressings should be to keep wound appropriately moist (i.e. moistening dry wounds or removing excess exudate/blood from wet wounds)
 - dry wounds → options include films and hydrogel dressings; require secondary dressing
 - light to moderately exudative → options include hydrocolloid dressing and hypertonic saline gauze
 - highly exudative → options include hydrofibre dressings, foam dressing, and hypertonic saline gauze
 - bleeding wounds → options include alginate dressings, as they have hemostatic properties
 - ♦ clean vs. infected wounds
 - clean wounds can be dressed with petroleum based gauze, which is non-adhering to epithelializing tissue; requires secondary dressing
 - infected wounds can be dressed with iodine gauze or silver-containing dressings
 - ♦ wide-based vs. cavitary/tunneling wounds
 - cavitary or tunnelling wounds (i.e. through a fascial layer) can be packed with saline-soaked (non-infected), betadine-soaked (infected) ribbon gauze, or other easily retrievable one-piece moisture providing dressing



Examples of Dressings

Films (Opsite®)
 Hydrogels (Intrasite®, Nu-gel®, Duoderm®)
 Hydrofibres (Aquacel®)
 Hydrocolloid (Duoderm®, Tegaderm®)
 Hypertonic saline gauze (Mesalt®)
 Foam (Mepilex®, Allevyn®)
 Alginates (Sorbsan®, Kaltostat®)
 Petroleum based gauze (Jelonet®)
 Silver dressings (AquacelAg®, Acticoat®)
 Iodine (Iodosorb®)

Reconstruction

SKIN GRAFTS

Definition

- a segment of skin detached from its blood supply at the donor site and dependent on revascularization from the recipient site

Donor Site Selection

- must consider size, hair pattern, texture, thickness of skin, and colour (facial grafts best if taken from “blush zones” above clavicle e.g. pre/post auricular or neck)
- partial thickness grafts usually taken from inconspicuous areas (e.g. buttocks, lateral thighs, etc.)



Reconstruction Ladder

- Secondary closure
- Primary closure
- Skin graft
- Local flap
- Regional flap
- Free tissue transfer

Partial Thickness Skin Graft Survival

- 3 phases of skin graft “take”
 1. plasmatic imbibition – diffusion of nutrition from recipient site (first 48 hours)
 2. inosculation – vessels in graft connect with those in recipient bed (day 2-3)
 3. neovascular ingrowth – graft revascularized (day 3-5)
- requirements for survival
 - bed: well-vascularized (unsuitable: bone, tendon, heavily irradiated, infected wounds, etc.)
 - contact between graft and recipient bed: fully immobile (decreased shearing and hematoma formation)
 - staples, sutures, splinting, and appropriate dressings (pressure) are used to prevent movement of graft and hematoma or seroma formation
 - site: low bacterial count ($<10^5$, to prevent infection)

Classification of Skin Grafts

1. by species
 - autograft: from same individual
 - allograft (homograft): from same species, different individual
 - xenograft (heterograft): from different species (e.g. porcine)
2. by thickness: (Table 3)

Table 3. Skin Grafts

	Split Thickness Skin Graft (STSG)	Full Thickness Skin Graft (FTSG)
Definition	Epidermis and part of dermis	Epidermis and all of dermis
Donor Site	More sites	Limited donor sites (full thickness skin loss, must be closed 1° or with STSG)
Healing of Donor Site	Re-epithelialization via dermal appendages in graft and wound edges	Primary closure or split thickness skin graft
Re-harvesting	~10 days (faster on scalp)	N/A
Graft Take	Easier; shorter nutrient diffusion distance	Lower rate of survival (thicker, slower vascularization)
Contraction	Less 1° contraction, greater 2° contraction (less with thicker graft)	Greater 1° contraction, less 2° contraction
Aesthetic	Poor	Good
Comments	Can be meshed for greater area (see below) Allows for extravasation of blood/serum	May use on face and fingers
Advantage	Takes well in less favourable conditions, can cover a larger area	Resists contraction, texture/pigment more normal
Disadvantage	Contracts significantly, abnormal pigmentation, high susceptibility to trauma	Requires well vascularized bed Must remove fat from graft before application
Uses	Large areas of skin, granulating tissue beds	Face (colour match), site where thick skin or decreased contracture is desired (e.g. finger)

- mesh graft
 - **advantages**
 - ♦ prevents accumulation of fluids (e.g. hematoma, seroma)
 - ♦ covers a larger area
 - ♦ best for contaminated recipient site
 - **disadvantages**
 - ♦ poor cosmesis (“alligator hide” appearance)
 - ♦ has significant contractures
- common reasons for graft loss: hematoma/seroma, infection, mechanical force (e.g. shearing, pressure)

OTHER GRAFTS

Table 4. Various Tissue Grafts

Graft Type	Use	Preferred Donor Site
Bone	Repair rigid defects	Cranial, rib, iliac, fibula
Cartilage	Restore contour of ear and nose	Ear, nasal septum, costal cartilage
Tendon	Repair damaged tendon	Palmaris longus, plantaris
Nerve	Conduit for regeneration across nerve gap	Sural, antebrachial cutaneous, medial brachial cutaneous
Vessel	Bridge vascular gaps	Forearm or foot vessels for small vessels, saphenous vein for larger vessels
Dermis	Contour restoration (\pm fat for bulk)	Thick skin of buttock or abdomen
Fat	Contour restoration	Abdomen, any area with fat available



Graft Contraction

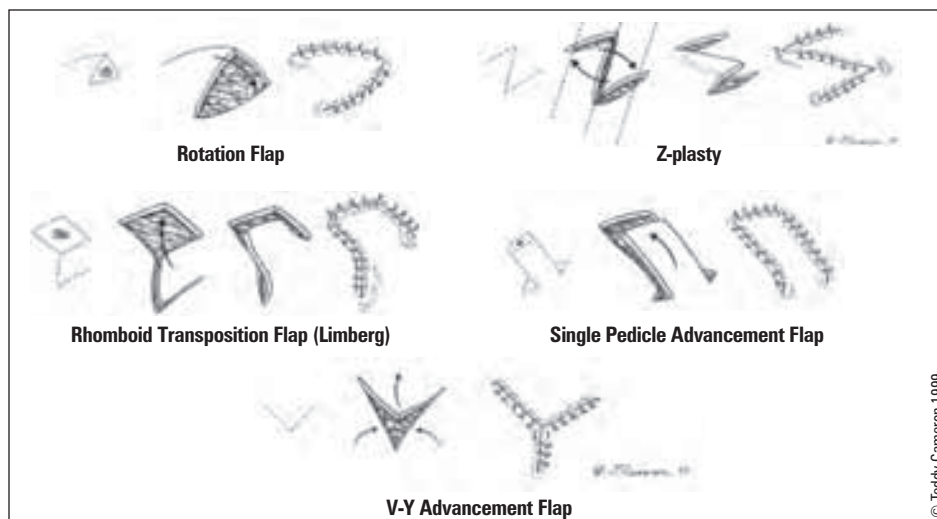
Primary – immediate reduction in size upon harvesting
Secondary – reduction in size once graft placed on wound bed

FLAPS

- **definition:** tissue transferred from one site to another with vascular supply (pedicle) intact (not dependent on neovascularization, unlike a graft)
- may consist of: skin, subcutaneous tissue, fascia, muscle, bone, other tissue (e.g. omentum)
- **classification:** based on blood supply to skin (random, axial) and anatomic location (local, regional, distant)
- **indications for flaps**
 - reconstruction – replaces tissue loss due to trauma or surgery
 - provides skin and temporary soft tissue coverage through which surgery can be carried out later
 - improves blood supply to poorly vascularized bed (e.g. bone)
- **main complication:** flap loss due to vascular thrombosis (in free flaps), flap necrosis caused by extrinsic compression (dressing too tight) or excess tension on wound closure, hematoma, seroma, infection, fat necrosis, poor flap design

Random Pattern Flaps (Figure 15)

- blood supply by dermal and subdermal plexus to skin and subdermal tissue with random vascular supply
- limited length:width ratio to ensure adequate blood supply (typically 2:1)
- flap choice is often a combination of available tissue and surgeon preference
- **types**
 - **rotation:** cover wounds of various sizes; common use: sacral pressure sores
 - **transposition**
 - **Z-plasty:** used to reorient a scar, lengthen the line of a scar or to break up a scar
 - **advancement flaps (single/bipedicle, V-Y, Y-V)**
 - ♦ V-Y flaps: wounds with lax surrounding tissue; the pedicle is the deep tissue underlying the flap

**Figure 15. Wound Care Flaps – Random Pattern****Axial Pattern Flaps (Arterialized)**

- flap contains a well defined artery and vein
- allows greater length: width ratio (5-6:1)
- **types**
 - **peninsular flap** – skin and vessel intact in pedicle (see Figure 16)
 - **island flap** – vessel intact, pedicle is better defined (see Figure 17)
 - **free flap** – vascular supply anastomosed at recipient site by microsurgical techniques
- can be sub-classified according to tissue content of flap:
 - e.g. musculocutaneous/myocutaneous [e.g. Transverse Rectus Abdominal Myocutaneous (TRAM)] vs. fasciocutaneous

Free Flaps

- transplanting expendable donor tissue from one part of the body to another by isolating and dividing a dominant artery and veins to a flap and performing a microscopic anastomosis between these and the vessels in the recipient wound
- survival rates >95%
- **types:** muscle and skin (common), bone, jejunum, omentum
 - e.g. radial forearm, scapular, latissimus dorsi

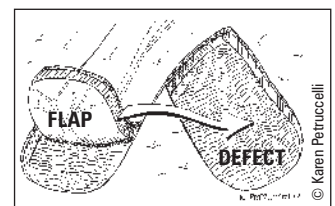
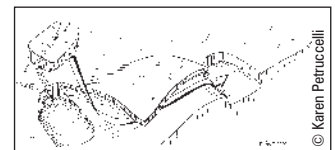
**Figure 16. Peninsular Axial Pattern Flap****Figure 17. Island Axial Pattern Flap**

Table 5. Free Flap Characteristics

Characteristic	Normal	Arterial Insufficiency	Venous Insufficiency
Colour	Pink	Pale	Purple or blue
Temperature	Warm	Cool	Warm or cool
Arterial Pulse (Doppler)	+	±	±
Turgor	Soft, but with tissue turgor	Decreased	Increased (i.e. tense)

Soft Tissue Infections

Erysipelas

Definition

- acute skin infection that is more superficial than cellulitis

Etiology

- typically caused by Group A β -hemolytic *Streptococcus* (GABHS)

Clinical Features

- intense erythema, induration, and **sharply demarcated borders** (differentiates it from other skin infections)

Treatment

- penicillin or first generation cephalosporin (e.g. cefazolin or cephalexin)

Table 6. Classification of Soft Tissue Infections by Depth

Erysipelas	Superficial with subcutaneous tissue involvement
Cellulitis	Full thickness with subcutaneous tissue involvement
Fasciitis	Fascia
Myositis	Muscle

Cellulitis

Definition

- non-suppurative infection of skin and subcutaneous tissues

Etiology

- skin flora most common organisms: *S. aureus*, β -hemolytic *Streptococcus*
- immunocompromised: Gram-negative rods and fungi

Clinical Features

- source of infection
 - trauma, recent surgery
 - PVD, diabetes – cracked skin in feet/toes
 - foreign bodies (IV, orthopaedic pins)
- systemic symptoms (fever, chills, malaise)
- pain, tenderness, edema, erythema with poorly defined margins, regional lymphadenopathy
- can lead to ascending lymphangitis (visible red streaking in skin proximal to area of cellulitis)

Investigations

- CBC, blood cultures
- culture and Gram stain wound/aspirate from wound if open wound
- plain radiographs if suspect foreign body or abscess
 - r/o bone invasion (osteomyelitis)

Treatment

- antibiotics: first line – cephalexin 500 mg PO q6h or dicloxacillin 500 mg PO q6h x 7 days if complicated (e.g. lymphangitis, DM) consider IV cefazolin 1-2 g q8h
- outline area of erythema to monitor success of treatment
- immobilize and splint (hands)



Cellulitis vs. Erysipelas
 Cellulitis: indistinct borders
 Erysipelas: sharp borders

Necrotizing Fasciitis

Definition

- rapidly spreading, very painful infection of the deep fascia with necrosis of tissues
- some bacteria create gas that can be felt as crepitus and be seen on x-rays
- infection spreads rapidly along deep fascial plane and is **limb and life threatening**

Etiology

- Type I: β -hemolytic *Streptococcus*
- Type II: polymicrobial (less aggressive)

Clinical Features

- **pain out of proportion to clinical findings and beyond border of erythema**, edema, tenderness, \pm crepitus (subcutaneous gas from anaerobes) \pm fever
- infection spreads very rapidly
- patients may look deceptively well at first, but may rapidly become very sick/toxic
- late findings:
 - skin turns dusky blue and black (secondary to thrombosis and necrosis)
 - induration, formation of bullae
 - cutaneous gangrene, subcutaneous emphysema

Investigations

- a **clinical diagnosis**
- CT scan only if suspect it is not necrotizing fasciitis (looking for abscess, myonecrosis, etc.)
- severely elevated CK: usually means myonecrosis (late sign)
- hemostat easily passed along fascial plane; fascial biopsy in equivocal situations

Treatment

- rigorous resuscitation
- multiple surgical debridements: remove all necrotic tissue, copious irrigation
- IV antibiotics: as appropriate for clinical scenario; consider penicillin 4 million IU IV q4h or clindamycin 900 mg IV q6h
- urgent consultation with infectious disease specialist is recommended



Soft tissue infections: Suspect necrotizing fasciitis with rapidly spreading erythema and edema. **Must demarcate** erythematous area on admission in order to determine amount of spread/rapidity of spread.

Ulcers

Lower Limb Ulcers

Traumatic Ulcers (Acute)

- failure of lesions to heal, usually due to compromised blood supply and unstable scar
- usually over bony prominence, \pm edema, \pm pigmentation changes, \pm pain
- treatment: debridement of ulcer and compromised tissue, reconstruction with local or distant flap, vascular status of limb must be assessed either clinically or radiographically

Non-Traumatic Ulcers (Chronic)

Table 7. Venous vs. Arterial vs. Diabetic Ulcers

Characteristic	Venous (70% vascular ulcers)	Arterial	Diabetic
Cause	Valvular incompetence Venous HTN	2° to small and/or large vessel disease Be aware of risk factors	Peripheral neuropathy: decreased sensation Atherosclerosis: decreased regional blood flow
History	Dependent edema, trauma Rapid onset \pm thrombophlebitis, varicosities	Arteriosclerosis, claudication Usually >45 years Slow progression	Diabetes mellitus Peripheral neuropathy
Distribution	Medial malleolus	Distal locations	Pressure point distribution
Appearance	Yellow exudates Granulation tissue	Pale/white, necrotic base \pm dry eschar covering	Necrotic base
Wound Margins	Irregular	Even ("punched out")	Irregular or "punched out" or deep
Depth	Superficial	Deep	Superficial/deep
Surrounding Skin	Venous stasis discolouration (brown)	Thin shiny dry skin, hairless, cool	Thin dry skin \pm hyperkeratotic border Hypersensitive/ischemic



Ankle-brachial index (ABI) in diabetics can be falsely normal due to incompressible arteries secondary to plaques/calcification.



All chronic ulcers require vascular studies and a vascular consult.

Table 7. Venous vs. Arterial vs. Diabetic Ulcers (continued)

Characteristic	Venous (70% vascular ulcers)	Arterial	Diabetic
Pulses	Normal distal pulses	Decreased distal pulses	Decreased pulses likely
Vascular Exam	ABI >0.9 Doppler; abnormal venous system	ABI <0.9 Pallor on elevation, rubor on dependency Delayed venous filling	ABI is inaccurately high Usually associated with arterial disease
Pain	Moderately painful Increased with leg dependency, decreased with elevation No rest pain	Extremely painful Decreased with dependency, increased with leg elevation and exercise (claudication) Rest pain	Painless No claudication or rest pain Associated paresthesia, anesthesia
Treatment	Leg elevation, rest Compression at 30 mmHg (stockings or elastic bandages) Moist wound dressings ± topical, systemic antibiotics ± skin grafts	Rest, no elevation, no compression Moist wound dressing ± topical and/or systemic antibiotics Modify risk factors (smoking, diet, exercise, etc.) Vascular surgical consultation Treat underlying conditions (DM, proximal arterial occlusion, etc.)	Control diabetes Careful wound care Foot care Orthotics Early intervention for infections (topical and/or systemic antibiotics) Vascular surgical consultation

Pressure Ulcers

Common Sites

- over bony prominences; 95% on lower body

Stages of Development

1. hyperemia – disappears 1 hour after pressure removed
2. ischemia – follows 2-6 hours of pressure
3. necrosis – follows >6 hours of pressure
4. ulcer – necrotic area breaks down – N.B. skin is like tip of an iceberg

Classification (National Pressure Ulcer Advisory Panel 2007)

Stage I: nonblanchable erythema present >1 hr after pressure relief, skin intact

Stage II: partial-thickness skin loss

Stage III: full-thickness skin loss into subcutaneous tissue, but not through fascia

Stage IV: through fascia into muscle, bone, tendon, or joint

- if an eschar is present, must fully debride before staging possible

Prevention

- good nursing care (clean dry skin, frequent repositioning), special beds or mattress (Kin Air®), proper nutrition, activity, early identification of individuals at risk (e.g. immobility, incontinence, paraplegia, etc.)

Treatment

- depends on individual patient and condition
- treat underlying medical issues including nutrition
- continue with preventative measures (pressure relief)
- wound debridement, moisture retentive or antimicrobial dressing, regular reassessment
- topical antimicrobials at treating physician's discretion, systemic antibiotics for infections
- assess for possible reconstruction

Complications

- cellulitis, osteomyelitis, sepsis, gangrene

Management of Skin Lesions

Skin Lesions

- see Dermatology, D6

Burns

Burn Injuries

Causal Conditions

- thermal (flame contact, scald)
- chemical
- radiation (UV, medical/therapeutic)
- electrical

Most Common Etiology

- children: scald burns
- adults: flame burns

Table 8. Skin Function and Burn Injury

Skin Function	Consequence of Burn Injury	Intervention Required
Thermoregulation	Prone to lose body heat	Must keep patient covered and warm
Control of fluid loss	Loss of large amounts of water and protein from the skin and other body tissues	Adequate fluid resuscitation is imperative
Mechanical barrier to bacterial invasion and immunological organ	High risk of infection	Antibiotic ointments (systemic if signs of specific infection present) Tetanus prophylaxis if necessary

Pathophysiology of Burn Wounds

- amount of tissue destruction is based on temperature, time of exposure, and specific heat of the causative agent (see Figure 18)
- **zone of hyperemia** – vasodilation from inflammation; entirely viable, cells recover within 7 days; contributes to systemic consequences seen with major burns
- **zone of stasis (edema)** – decreased perfusion; microvascular sludging and thrombosis of vessels results in progressive tissue necrosis → cellular death in 24-48 hours without proper treatment
 - factors favoring cell survival: moist, aseptic environment, rich blood supply
 - zone where appropriate early intervention has most profound effect in minimizing injury
- **zone of coagulation (ischemia)** – no blood flow to tissue → irreversible cell damage → cellular death/necrosis

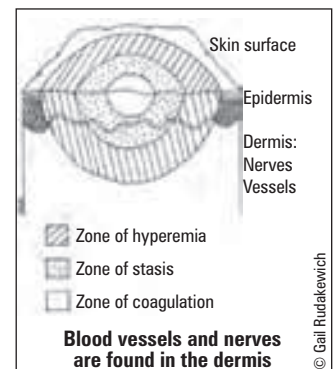


Figure 18. Zones of Thermal Injury

Diagnosis and Prognosis

- burn size (see Figure 19)
 - % of total body surface area (TBSA) burned – rule of 9's for 2° and 3° burns only (children <10 years old use Lund-Browder chart – see Figure 20)
 - for patchy burns, surface area covered by patient's palm (fingers closed) represents approximately 1% of TBSA
- age: more complications if <3 or >60 years old
- depth: difficult to assess initially – history of etiologic agent and time of exposure helpful (see Table 9)
- location: face and neck, hands, feet, perineum are critical areas requiring special care of a burn unit (see further discussion on *Indications for Transfer to Burn Centre*)
- inhalation injury: can severely compromise respiratory system
- associated injuries (e.g. fractures)
- comorbid factors (e.g. concurrent disability, alcoholism, seizure disorders, chronic renal failure) can exacerbate extent of injury

Prognosis best determined by burn size (TBSA), age of patient, presence/absence of inhalation injury.

Circumferential burns can restrict respiratory excursion and/or blood flow to extremities and require escharotomy.

TBSA does not include areas with 1° burns.

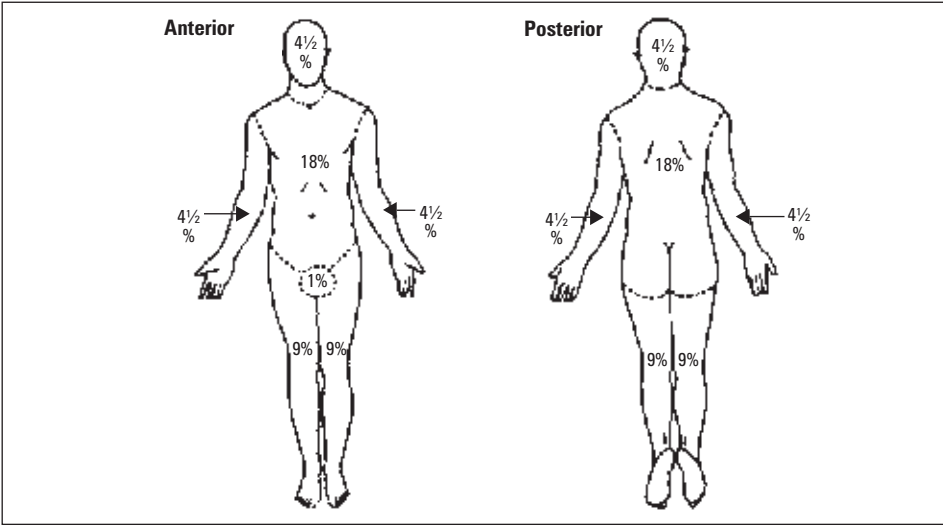


Figure 19. Rule of 9's for Total Body Surface Area (TBSA)

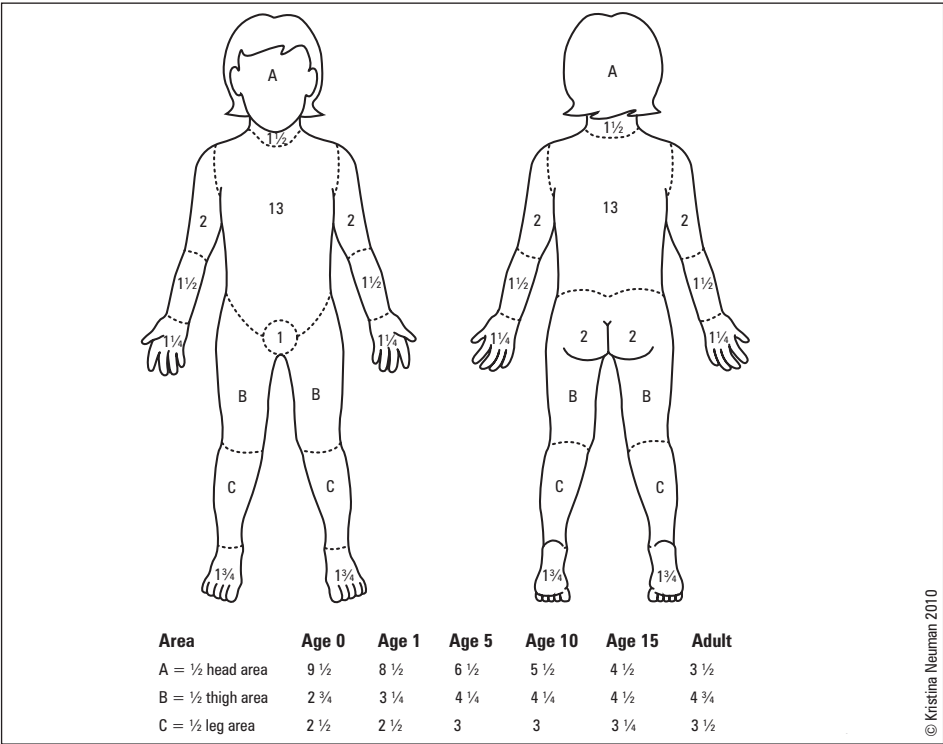


Figure 20. Lund-Browder Diagram

Table 9. Burn Depth (1st, 2nd, 3rd degree)

Nomenclature	Traditional Nomenclature	Depth	Clinical Features
Erythema/Superficial	First degree	Epidermis	Painful, sensation intact, erythema, blanchable
Superficial-Partial Thickness	Second degree	Into superficial dermis	Painful, sensation intact, erythema, blisters with clear fluid, blanchable, hair follicles present
Deep-Partial Thickness	Second degree	Into deep (reticular) dermis	Insensate, difficult to distinguish from full thickness, does not blanch, some hair follicles still attached, softer than full thickness burn
Full Thickness	Third degree Fourth degree	Through epidermis and dermis Injury to underlying tissue structures (e.g. muscle, bone)	Insensate (nerve endings destroyed), hard leathery eschar that is black, grey, white, or cherry red in colour, hairs do not stay attached, may see thrombosed veins

Indications for Transfer to Burn Centre

American Burn Association Criteria

- total 2° and 3° burns >10% TBSA in patients <10 or >50 years of age
- total 2° and 3° burns >20% TBSA in patients any age
- 3° burns/full thickness >5% TBSA in patients any age
- 2°, 3° or chemical burns posing a serious threat of functional or cosmetic impairment (i.e. circumferential burns, burns to face, hands, feet, genitalia, perineum, major joints)
- inhalation injury (may lead to respiratory distress)
- electrical burns, including lightning (internal injury underestimated by TBSA)
- burns associated with major trauma/serious illness

Acute Care of Burn Patients

- adhere to ATLS protocol
- resuscitation using Parkland formula to restore plasma volume and cardiac output
 - 4 cc Ringer's/kg/% TBSA over first 24 hours (1/2 within first 8 hours of sustaining burn, 1/2 in next 16 hours)
- extra fluid administration required if
 - burn >80% TBSA
 - 4° burns
 - associated traumatic injury
 - electrical burn
 - inhalation injury
 - delayed start of resuscitation
 - pediatric burns
- monitor resuscitation
 - urine output is best measure – maintain at >0.5 cc/kg/hr (adults) and 1.0 cc/kg/hour (children <12 years)
 - maintain a clear sensorium, HR <120/minute, mean BP >70 mmHg
- burn specific care
 - relieve respiratory distress – intubation and/or escharotomy (see sidebar)
 - prevent and/or treat burn shock – 2 large bore IVs
 - identify and treat immediate life-threatening conditions (e.g. inhalation injury, CO poisoning)
 - determine BSA affected 1st, since depth is difficult to determine initially (easier to determine after 24 hours)
- tetanus prophylaxis if needed
 - all patients with burns >10% TBSA, or deeper than superficial partial thickness, need 0.5 ml tetanus toxoid
 - also give 250 U of tetanus Ig if prior immunization is absent/unclear, or the last booster >10 yrs ago
- baseline laboratory studies (Hb, U/A, BUN, CXR, electrolytes, ECG, cross-match, ABG, carboxyhemoglobin)
- cleanse, debride, and treat the burn injury (antimicrobial dressings)
- early excision and grafting important for outcome



Signs of CO Poisoning

- Headache
- Confusion
- Coma
- Arrhythmias



Inhalation Injuries 101

1. Indicators of Inhalation Injury
 - Injury in a closed space
 - Facial burn
 - Singed nasal hair/eyebrows
 - Soot around nares/oral cavity
 - Hoarseness
 - Conjunctivitis
 - Tachypnea
 - Carbon particles in sputum
 - Elevated blood CO levels (i.e. brighter red)
2. Suspected inhalation injury requires immediate intubation due to impending airway edema. Failure to diagnose inhalation injury can result in airway swelling and obstruction, which, if untreated, can lead to death.
3. Neither CXR or ABG can be used to rule out inhalation injury.
4. Direct bronchoscopy now used for diagnosis

Respiratory Problems

- 3 major causes
 - burn eschar encircling chest
 - ♦ distress may be apparent immediately
 - ♦ perform escharotomy to relieve constriction
 - carbon monoxide (CO) poisoning
 - ♦ may present immediately or later
 - ♦ treat with 100% O₂ by facemask (decreases half-life of carboxyhemoglobin from 210 to 59 minutes) until carboxyHb <10%
 - smoke inhalation leading to pulmonary injury
 - ♦ chemical injury to alveolar basement membrane and pulmonary edema (insidious onset)
 - ♦ risk of pulmonary insufficiency (up to 48 h) and pulmonary edema (48-72 h)
 - ♦ watch for secondary bronchopneumonia (3-25 days) leading to progressive pulmonary insufficiency
 - ♦ intubate patient with any signs of inhalation injuries

Table 10. Burn Shock Resuscitation (Parkland Formula)

Hour 0-24	4 cc Ringer's/kg/% TBSA with 1/2 of total 0-8 h and 1/2 of total 8-24 h
Hour 24-30	0.35-0.5 cc plasma/kg/%TBSA
>Hour 30	D5W at rate to maintain normal serum sodium

* do not forget to add maintenance fluid to resuscitation

Meta-Analysis of Early Excision of Burns
Burns 2006; 32:145-150.
Purpose: To establish if early excision and grafting is superior (or equivalent) to conservative treatment and delayed grafting once the burn eschar has separated.
Method/Population: A literature review was completed seeking prospective randomized controlled trials comparing early excision (<7 days) and immediate grafting against treatment with dressings followed by grafting post-eschar separation. All ages and burn severities were included. Outcomes were mortality, blood transfusions, wound healing time and length of hospital stay.
Results: A total of 361 patients from 7 randomized controlled trials were included in the meta-analysis. 180 patients received early intervention and 181 received conservative management. There was no significant difference in mortality in patients with inhalational injury. Early excision and grafting in patients without inhalational injury resulted in significantly reduced mortality (RR 0.36, p<0.05) and decreased length of hospitalization by 8.89 days (p<0.05). The number of patients requiring blood transfusion was significantly higher with early excisional management (SMD 1.65, p<0.05). There was no significant difference in wound healing time between the two groups.
Conclusion: Early excision of burns (<7 days) is beneficial in reducing mortality in patients without inhalational injury, along with reducing length of time spent in hospital.

Burn Wound Healing

Table 11. Burn Wound Healing

Depth	Healing
First degree	No scarring. Complete healing
Second degree (Superficial partial)	Spontaneously re-epithelialize in 7 to 14 days from retained epidermal structures ± residual skin discolouration Hypertrophic scarring uncommon. Grafting rarely required
Deep second degree (Deep partial)	Re-epithelialize in 14-35 days from retained epidermal structures Hypertrophic scarring frequent Grafting recommended to expedite healing
Third Degree (Full thickness)	Re-epithelialize from the wound edge Grafting necessary to replace dermal integrity, limit hypertrophic scarring
Fourth Degree	Re-epithelialize from the wound edge Grafting necessary to replace dermal integrity Must ensure viable bed to graft onto

Treatment


- 3 stages
 1. assessment – depth determined
 2. management – specific to depth of burn
 3. rehabilitation
- first degree
 - treatment aimed at comfort
 - ♦ topical creams (pain control, keep skin moist) ± aloe
 - ♦ oral NSAIDs (pain control)
- superficial second degree
 - daily dressing changes with topical antibiotics, polysporin, may use a temporary biological or synthetic covering to close the wound; leave blisters intact unless circulation impaired
- deep second degree and third degree
 - prevent infection and sepsis (significant cause of death in burn patients)
 - ♦ most common organisms: *S. aureus*, *P. aeruginosa* and *C. albicans*
 - day 1-3: Gram-positive
 - day 3-5: Gram-negative (*Proteus*, *Klebsiella*)
 - ♦ topical antimicrobials: prevent bacterial infection (from skin flora, gut flora or caregiver) and secondary sepsis (Table 12)
 - remove dead tissue
 - ♦ surgically debride necrotic tissue, excise to viable (bleeding) tissue

Table 12. Topical Antibiotic Therapy

Antibiotic	Pain with Application	Penetration	Adverse Effects
Silver nitrate (0.5% solution)	None	Minimal	May cause methemoglobinemia, stains (black), leaches sodium from wounds
Silver sulfadiazine (cream) (Sulfamylon®)	Minimal	Medium, does not penetrate eschar	Slowed healing, leukopenia, mild inhibition of epithelialization
Mafenide acetate (solution/cream) (Silvadene®)	Moderate	Well, penetrates eschar	Mild inhibition of epithelialization, may cause metabolic acidosis with wide application

- important to obtain early wound closure
- initial dressing should decrease bacterial proliferation
- indication for skin graft: deep 2° or 3° burn > size of a quarter
- prevention of wound contractures: pressure dressings, joint splints, early physiotherapy

Other Considerations in Burn Management


 Pneumonia is the most common cause of death in burn patients.

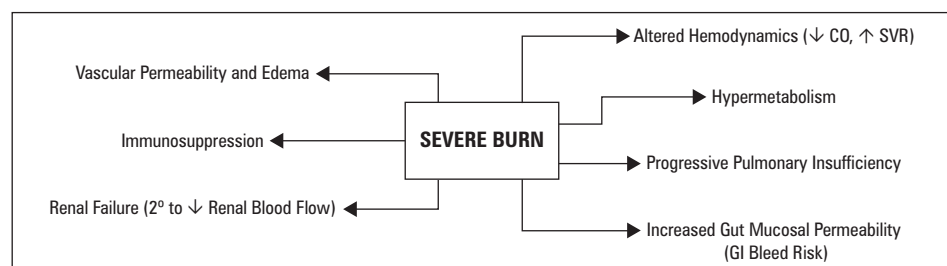


Figure 21. Systemic Effects of Severe Burns

- nutrition
 - hypermetabolism: TBSA >40% have BMR 2-2.5x predicted
 - calories, vitamin C, vitamin A, Ca, Zn, Fe
- immunosuppression and sepsis
 - must keep bacterial count <10⁵ bacteria/g of tissue (blood culture may not be positive)
 - signs of sepsis: sudden onset of hyper/hypothermia, unexpected CHF or pulmonary edema, development of ARDS, ileus >48 hours post-burn, mental status changes, azotemia, thrombocytopenia, hypofibrinogenemia, hyper/hypoglycemia (especially if burn >40% TBSA)
- gastrointestinal (GI) bleed may occur with burns >40% TBSA (usually subclinical)
 - treatment: tube feeding or NPO, antacids, H₂ blockers (preventative)
- renal failure secondary to under resuscitation, drugs, myoglobin, etc.
- progressive pulmonary insufficiency
 - can occur after: smoke inhalation, pneumonia, cardiac decompensation, sepsis
- wound contracture and hypertrophic scarring
 - largely preventable with timely wound closure, splinting, pressure garments and physiotherapy

Special Considerations

CHEMICAL BURNS

- major categories: acid burns, alkaline burns, phosphorous burns, chemical injection injuries
- common agents: cement, hydrofluoric acid, phenol, tar
- mechanism of injury: chemical solutions coagulate tissue protein leading to necrosis
 - acids → coagulation necrosis
 - alkalines → saponification followed by liquefactive necrosis
- severity related to: type of chemical (alkali worse than acid), temperature, volume, concentration, contact time, site affected, mechanism of chemical action, degree of tissue penetration
- burns are deeper than initially appear and may progress with time

Treatment (general)

- ABCs, monitoring
- remove contaminated clothing and brush off any dry powders before irrigation
- irrigation with water for 1-2 h under low pressure
- inspect eyes, if affected: wash with saline and refer to ophthalmology
- inspect nails, hair and webspaces
- correct metabolic abnormalities and tetanus prophylaxis if necessary
- local wound care after 12 hours initial dilution (debridement)
- wound closure same as for thermal burn
- beware of underestimated fluid resuscitation, renal, liver, and pulmonary damage

ELECTRICAL BURNS

- depth of burn depends on voltage and resistance of the tissue (injury more severe in tissues with high resistance)
- often presents as small punctate burns on skin with extensive deep tissue damage which requires debridement
- electrical burns require ongoing monitoring as latent injuries can occur
- watch for system specific damages and abnormalities:
 - abdominal: intraperitoneal damage
 - bone: fractures and dislocations especially of the spine and shoulder
 - cardiopulmonary: anoxia, ventricular fibrillation, arrhythmias
 - muscle: myoglobinuria indicates significant muscle damage → compartment syndrome
 - neurological: seizures and spinal cord damage
 - ophthalmology: cataract formation (late complication)
 - renal: acute tubular necrosis (ATN) resulting from toxic levels of myoglobin and hemoglobin
 - vascular: vessel thrombosis → tissue necrosis (increased Cr, K and acidity), decrease in RBC (beware of hemorrhages/delayed vessel rupture)

Treatment

- ABCs, primary and secondary survey, treat associated injuries
- monitor: hemochromogenuria, compartment syndrome, urine output
- wound management: topical agent with good penetrating ability (silver sulfadiazine or mafenide acetate)
- debride non-viable tissue early and repeat prn (every 48 h) to prevent sepsis
- amputations frequently required

FROSTBITE

- see Emergency Medicine, ER45



Speed is essential in the management of chemical burns as chemicals can continue to cause damage until they are removed or neutralized.



Tar: remove with repeated application of petroleum-based antibiotic ointments (e.g. Polysporin®).



Treatment (specific)

Acid burns: dilute solution of sodium bicarbonate following water irrigation
Hydrofluoric acid: water irrigation; clip fingernails to avoid acid trapping; topical calcium gel ± subcutaneous injection of calcium gluconate ± 10% calcium gluconate IV depending on amount of exposure and pain
Sulfuric acid: treat with soap/lime prior to irrigation, as direct water exposure produces extreme heat



Tissue Resistance to Electrical Current:

nerve < vessel/blood < muscle < skin
 < tendon < fat < bone

Vessels

- often associated with nerve injury (anatomical proximity)
- control bleeding with direct pressure and hand elevation
- if digit devascularized, optimal repair within 6 hours
- dress, immobilize, and splint hand with finger tips visible
- monitor colour, capillary refill, skin turgor, fingertip temperature post-revascularization

Tendons

- most tendon lacerations require primary repair
- many extensors are repaired in the emergency room, flexors in the operating room within 2 weeks
- avoid excessive immobilization (specific protocols for flexors, 2-3 weeks for extensors) to minimize stiffness and facilitate rehabilitation

**Compartment Syndrome**

Watch out for these signs with a closed or open injury: tense, painful extremity (worse on passive stretch), distal pulselessness (often late in process), paresthesia/paralysis, and contracture (irreversible ischemia).

Intracompartmental pressures can be measured, but a clinical diagnosis is an indication for an emergent fasciotomy. If untreated, end result is ischemic contracture of the extremity (Volkmann's contracture).

Hand Infections

Principles

- trauma is most common cause
- 5 cardinal signs: *rubor* (red), *calor* (hot), *tumour* (swollen), *dolor* (painful) and *functio laesa* (loss of function)
- 90% caused by Gram-positive organisms
- most common organisms (in order) – *S. aureus*, *S. viridans*, Group A *Streptococcus*, *S. epidermidis*, and *Bacteroides melaninogenicus* (MRSA becoming more common)

TYPES OF INFECTIONS**Deep Palmar Space Infections**

- uncommon, involve thenar or mid-palm, treated in OR

Felon

- **definition:** subcutaneous abscess in the fingertip that commonly occurs following severe paronychia or a puncture wound into the pad of digit; may be associated with osteomyelitis
- **treatment:** elevation, warm soaks, cloxacillin 500 mg PO q6h (if in early stage); if obvious abscess then I&D and PO cloxacillin

Flexor Tendon Sheath Infection

- *Staph* > *Strep* > Gram-Negative Rods
- **definition:** acute suppurative tenosynovitis commonly caused by a penetrating injury and can lead to tendon necrosis and rupture if not treated
- **clinical features:** Kanavel's 4 cardinal signs:
 1. point tenderness along flexor tendon sheath (earliest and most important)
 2. severe pain on passive extension of DIP (second most important)
 3. fusiform swelling of entire digit
 4. flexed posture (increased comfort)
- **treatment**
 - OR incision and drainage, irrigation, IV antibiotics, and resting hand splint until infection resolves

Herpetic Whitlow

- HSV-1, HSV-2
- **definition:** painful vesicle(s) around fingertip
- often found in medical/dental personnel and children
- **clinical features:** can be associated with fever, malaise and lymphadenopathy
- patient is infectious until lesion has completely healed
- **treatment:** routine culture and viral prep protection (cover), consider oral acyclovir

Paronychia

- acute = *Staph*; chronic = *Candida*
- **definition:** infection (granulation tissue) of soft tissue around fingernail (beneath eponychial fold)
- **etiology**
 - acute paronychia – a “hangnail”, artificial nails, and nail biting
 - chronic paronychia – prolonged exposure to moisture
- **treatment**
 - acute paronychia – warm compresses and cephalexin 500 mg PO q6h ± drainage if abscess present
 - chronic paronychia – anti-fungals with possible debridement and marsupialization, removal of nail plate

Amputations

Hand or Finger

- emergency management: injured patient and amputated part require attention
 - **patient:** x-rays, NPO, clean wound and irrigate with NS, dress stump with nonadherent, cover with dry sterile dressing, tetanus and antibiotic prophylaxis (cephalosporin/erythromycin)
 - **amputated part:** x-rays, gently irrigate with RL, wrap amputated part in a NS/RL soaked sterile gauze and place inside waterproof plastic bag, place in a container, then place container on ice
- **indications for replantation**
 - **age:** children often better results than adults
 - **level of injury:** proximal, thumb and multiple digit amputations are higher priority
 - **nature of injury:** guillotine injuries have a better potential; avulsion and crush injuries are relative contraindications to replant
- if replant contraindicated manage stump with revision amputation
 - would only allow a fingertip injury to heal by secondary intention

Tendons

Common Extensor Tendon Deformities

Table 14. Extensor Tendon Deformities

Injury	Definition	Zone	Etiology/Clinical Features	Treatment
Mallet Finger	DIP flexed with loss of active extension (see Figure 23)	1	Forced flexion of the extended DIP joint leading to extensor tendon rupture at DIP joint (e.g. sudden blow to tip of the finger)	Splint DIP in extension for 6 weeks followed by 2 weeks of night splinting. If inadequate improvement after 6 weeks, check splinting routine and recommend 4 more weeks of continuous splinting
Boutonniere Deformity	PIP flexed, DIP hyperextended (see Figure 24)	3	Injury or disease affecting the extensor tendon insertion into the dorsal base of the middle phalanx. Associated with rheumatoid arthritis (RA) or trauma (laceration, volar dislocation, acute forceful flexion of PIP)	Splint PIP in extension and allow active DIP motion
Swan Neck Deformity	PIP hyperextended, DIP flexed (see Figure 25)	3	Trauma (PIP volar plate injury). Associated with RA and old, untreated mallet deformity	Splint to prevent PIP hyperextension or DIP flexion. Consider arthrodesis/arthroplasty

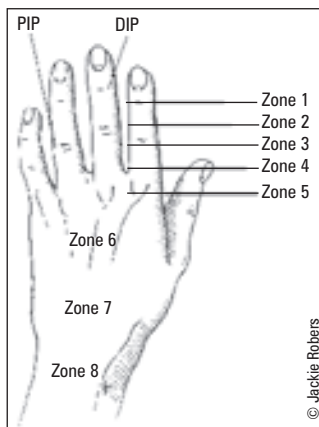


Figure 22. Zone of Extensor Tendon Injury (Odd numbered zones fall over a joint)

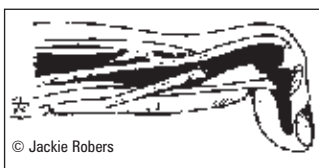


Figure 23. Mallet Finger Deformity

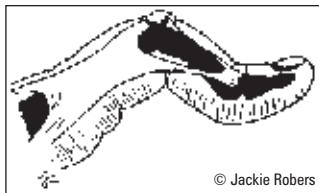


Figure 24. Boutonniere Deformity

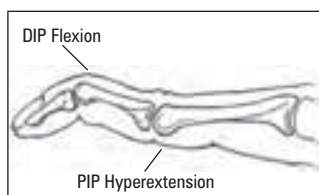


Figure 25. Swan Neck Deformity

De Quervain's Tenosynovitis (zone 7; most common cause of radial wrist pain)

- **definition:** inflammation in 1st extensor compartment (APL and EPB)
- **clinical features:**
 - +ve Finkelstein's test (pain over the radial styloid induced by making fist, with thumb in palm, and ulnar deviation of wrist)
 - pain localized to the 1st extensor compartment
 - tenderness and crepitation over radial styloid may be present
 - differentiate from CMC joint arthritis (CMC joint arthritis will have a positive grind test, whereby crepitus and pain are elicited by axial pressure to the thumb)
- **treatment:**
 - **mild:** NSAIDs, splinting and steroid injection into the tendon sheath (successful in over 60% of cases)
 - **severe:** surgical release of stenotic tendon sheaths (APL and EPB); remember there may be 2 or more sheaths

Ganglion Cyst (zone 7)

- **definition:**
 - fluid-filled synovial lining that protrudes between carpal bones or from a tendon sheath; most commonly carpal in origin
 - most common soft tissue tumour of hand and wrist (60% of masses)
- **clinical features:**
 - most common around scapholunate ligament junction
 - 3 times more common in women than in men
 - more common in younger individuals
 - can be large or small – may drain internally so size may wax and wane
 - often non-tender although tenderness increased when cyst smaller (from increased pressure within smaller cyst sac)

- **treatment:**
 - conservative treatment: watch and wait
 - aspiration (recurrence rate 65%)
 - consider operative excision of cyst and stalk (recurrence is possible)
 - steroids if painful

Common Flexor Tendon Deformities (see Figure 26)

- flexor tendon zones (important for prognosis of tendon lacerations)
- “no-man’s land”:
 - between distal palmar crease and mid-middle phalanx
 - zone where superficialis and profundus lie ensheathed together
 - recovery of glide very difficult after injury

Stenosing Tenosynovitis (trigger finger/thumb)

- **definition:** inflammation of synovium causes size discrepancy between tendon and sheath/pulley (most commonly at A-1 pulley) = locking of thumb or finger in flexion/extension
- **etiology:** idiopathic or associated with RA, diabetes, hypothyroidism and gout
- **clinical features:**
 - thumb, ring and long fingers most commonly affected
 - patient complains of catching, snapping or locking of affected finger
 - tenderness to palpation/nodule at palmar aspect of MCP over A1 pulley
 - women are 4 times more likely than men to be affected
- **conservative treatment:**
 - NSAIDs
 - steroid injection
 - surgical flexor tendon release
 - injections less likely to be successful in patients with DM or symptoms greater than 6 months
- **surgical treatment:**
 - incise A-1 flexor tendon pulley to permit unrestricted, full active finger motion



A2 and A4 pulleys are most important for function; prevent bowstringing of tendons.

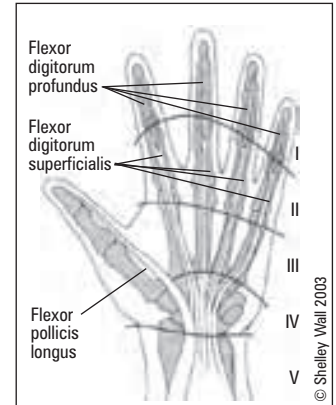


Figure 26. Zones of the Flexor Tendons

Fractures and Dislocations

- for fracture principles, see Orthopaedics, OR5

FRACTURES

- about 90% of hand fractures are stable in flexion (lock/prevent extension)
- **position of function** (like a hand holding a pop can) (see Figure 27):
 - wrist extension 15°
 - MCP flexion 45°
 - IP flexion (slight)
 - thumb abduction/rotation
 - contraindications: post repair of flexor tendons, median/ulnar nerve injury
- **position of safety** (see Figure 28):
 - wrist extension 45° (position most beneficial for hand function if immobilized)
 - MCP flexion 60° (maximal collateral ligament stretch)
 - PIP and DIP in full extension (maximal volar plate origin stretch)
 - thumb abduction and opposition (functional position)
- stiffness secondary to immobilization is the most important complication; Tx = early motion



Figure 27. Position of Function



Figure 28. Position of Safety

Distal Phalanx Fractures

- most commonly fractured bone in the hand
- usual mechanism is crush injury and thus accompanied by soft tissue injury
- subungual hematoma is common and must be decompressed if painful or nail removed
- treatment consists of 3 weeks of digital splinting (with IP joint movement preserved)

Proximal and Middle Phalanx Fractures

- check for: rotation, scissoring (overlap of fingers on making a fist), shortening of digit
- undisplaced or minimally displaced – closed reduction (if extra-articular) buddy tape to neighbouring stable digit, elevate hand, motion in guarded fashion 10-14 days post injury
- displaced, non-reducible or not stable with closed reduction – percutaneous pins (K-wires) or ORIF, and splint

Metacarpal Fractures

- generally accept varying degrees of deviation before reduction required: up to 10° (D2), 20° (D3), 30° (D4), or 40° (D5)
- **Boxer's fracture (extra-articular):** acute angulation of neck of metacarpal of little finger into palm (see Figure 29)
 - mechanism: blow on the distal-dorsal aspect of closed fist
 - loss of prominence of metacarpal head, volar displacement of head
 - check for scissoring of fingers on making a fist

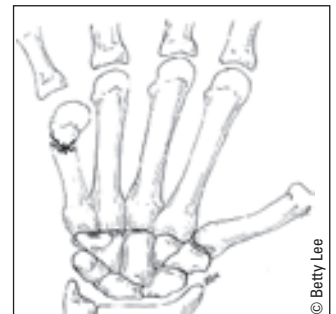


Figure 29. Boxer's Fracture

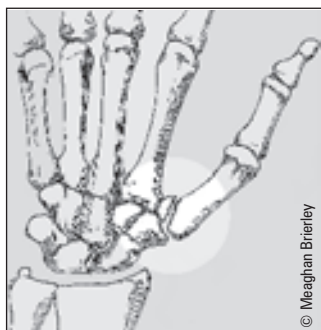


Figure 30. Bennett's Fracture



Figure 31. Rolando's Fracture

- up to 30-40° angulation may be acceptable
- closed reduction should be considered to decrease the angle
- if stable ulnar gutter splint x 3 weeks with PIP and DIP joints free
- **Bennett's fracture (intra-articular):** fracture/dislocation of the base of the thumb metacarpal (see Figure 30)
 - unstable fracture
 - abductor pollicis longus pulls MC shaft proximally and radially causing adduction of thumb
 - treat with percutaneous pinning, thumb spica x 6 weeks
- **Rolando's fracture (intra-articular):** T- or Y-shaped fracture of the base of the thumb metacarpal (see Figure 31)
 - treat with open reduction, internal fixation (ORIF) with K-wire

DISLOCATIONS

- must be reduced as soon as possible

PIP and DIP Dislocations (PIP more common than DIP)

- usually dorsal dislocation (commonly from hyperextension)
- if closed dislocation: closed reduction and splinting (30° flexion for PIP and full extension for DIP) or buddy taping and early mobilization (prolonged immobilization causes stiffness)
- open injuries are treated with wound care, closed or open reduction and antibiotics

MCP Dislocations (relatively rare)

- dorsal dislocations much more common than volar dislocations
- dorsal dislocation of proximal phalanx on metacarpal head; most commonly index finger (hyperextension)
- two types of dorsal dislocation:
 - simple (reducible with manipulation) – treat with 2 weeks of splinting at 30° MCP flexion
 - complex (volar plate blocks reduction) – treat with open reduction and A1 pulley release + extension-blocking splint at 30° flexion (2 weeks) then 10° flexion (2 weeks)

Ulnar Collateral Ligament (UCL) Injury

- forced abduction of thumb (e.g. ski pole injury)
- **skier's thumb:** acute UCL injury
- **gamekeepers thumb:** chronic UCL injury
- **evaluation:** radially deviate joint in full extension and at 30° flexion and compare with non-injured hand. UCL rupture is presumed if injured side deviates more than 30° in full extension or more than 15° in flexion
- **Stener's lesion:** the UCL has bony attachments to the adductor aponeurosis and the proximal ligament can displace while the distal attachment remains deep to the aponeurosis, forming a barrier that blocks healing and leads to chronic instability; requires surgery

Dupuytren's Disease

Definition

- contraction of longitudinal palmar fascia, forming nodules (usually painless), fibrous cords and eventually flexion contractures at the MCP and interphalangeal joints (see Figure 32)
- flexor tendons not involved
- Dupuytren's diathesis – early age of onset, strong family history, and involvement of sites other than palmar aspect of hand

Epidemiology

- genetic disorder (unusual in patients from African and Asian countries, high incidence in northern Europeans), men > women, often presents in 5th-7th decade of life, associated with but not caused by alcohol use and diabetes

Clinical Features

- order of digit involvement (most common to least common): ring > little > long > thumb > index
- may also involve feet (Lederhosen's) and penis (Peyronie's – see [Urology](#), U29)

Treatment

- stages:
 1. palmar pit or nodule – no surgery
 2. palpable band/cord with no limitation of extension of either MCP or PIP – no surgery
 3. lack of extension at MCP or PIP – surgical fasciectomy indicated
 4. irreversible periarticular joint changes/scarring – surgical treatment possible but poorer prognosis compared to stage 3

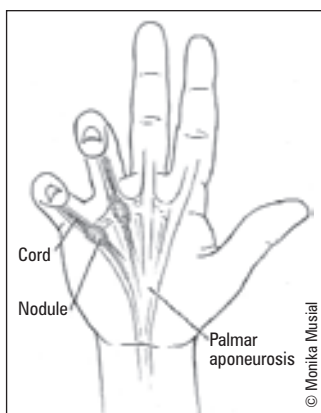


Figure 32. Dupuytren's Disease



Accuracy of the Clinical Assessment for Carpal Tunnel Syndrome

Hand Surgery Update 1996; p.223

1. Phalen's:
 - Sensitivity: 0.75 Specificity: 0.47
2. Tinel's:
 - Sensitivity: 0.60 Specificity: 0.67
3. Carpal Tunnel Compression Test:
 - Sensitivity: 0.87 Specificity: 0.90

- indications for percutaneous release:
 - functional impairment
 - MCP joint contractures $>30^\circ$
 - any PIP contracture
 - rapidly progressive disease
- may recur, especially in Dupuytren's diathesis

Carpal Tunnel Syndrome (CTS)

Definition

- median nerve compressed by nearby anatomic structures

Etiology

- median nerve entrapment at wrist
- primary cause is idiopathic
- secondary causes: space occupying lesions (tumours, hypertrophic synovial tissue, fracture callus, and osteophytes), metabolic and physiological (pregnancy, hypothyroidism, and rheumatoid arthritis), infections, neuropathies (associated with diabetes mellitus or alcoholism), and familial disorders
- job/hobby related repetitive trauma, especially forced wrist flexion

Epidemiology

- female:male = 4:1, **most common entrapment neuropathy**

Clinical Features

- sensory loss in median nerve distribution i.e. radial 3.5 digits (see Figure 3)
- discriminative touch often lost first
- classically, patient awakened at night with numb/painful hand, relieved by shaking/dangling/rubbing
- decreased light touch, 2-point discrimination, especially fingertips
- advanced cases: thenar wasting/weakness
- \pm Tinel's sign (tingling sensation on percussion of nerve)
- \pm Phalen's sign (wrist flexion induces symptoms)

Investigations

- a clinical diagnosis
- nerve conduction velocities (NCV) and EMG may confirm, but do not exclude, the diagnosis

Treatment

- avoid repetitive wrist and hand motion, wrist splints when repetitive wrist motion required
- conservative: night time splinting to keep wrist in neutral position
- medical: NSAIDs, local corticosteroids injection, oral corticosteroids
- surgical decompression: transverse carpal ligament incision to decompress median nerve
- indications for surgery: numbness and tingling \pm sensory loss, weakness \pm muscle atrophy, unresponsive to conservative measures
- complications: injury to median motor branch, palmar cutaneous branch or superficial transverse vascular arch, local pain (pillar pain), scar

Rheumatoid Hand

General Principles

- non-surgical treatments form the foundation in the management of the rheumatoid hand
- surgery only for patients whose goals (improved cosmesis or function) may be achieved

Surgical Treatment of Common Problems

- synovitis: requires tendon repair if ruptured; can lead to carpal tunnel syndrome and trigger finger
- ulnar drift: MCP arthroplasty, resection of distal ulna, soft tissue reconstruction around wrist
- thumb deformities: can be successfully treated by arthrodeses (surgical fixation of joint to promote bone fusion)

Development and Validation of Diagnostic Criteria for Carpal Tunnel Syndrome

J Hand Surg, 2006, Vol 31 No. 6 p.919

Purpose: To develop a clinical diagnostic criteria for carpal tunnel syndrome that modeled the clinical diagnostic practices of experts.

Methods: Out of 57 clinical findings associated with CTS, eight were ranked highly by a panel of expert clinicians. Using 256 case histories, a panel of experts decided whether a case did or did not have a diagnosis of CTS. This diagnosis represented the dependent variable for a logistic regression model, to which the eight clinical findings were applied. The regression model was then validated against the consensus of a second panel on the diagnosis of CTS for the case histories.

Results: The correlation between the probability of CTS predicted by the regression model and the panel of clinicians was 0.71. The following is the final list of unweighted clinical diagnostic criteria that contributed significantly to the model:

1. Numbness and tingling in median nerve distribution
2. Nocturnal numbness
3. Weakness and/or atrophy of the thenar musculature
4. Tinel's sign
5. Phalen's test
6. Loss of 2-point discrimination



Radiographic Evolution of the Rheumatoid Hand

Earliest sign: erosion of the ulnar styloid

Progression: characterized by symmetrical joint space narrowing and erosions of the carpal bones, MCP and PIP (with DIP relatively spared)

Late stage: Swan neck and Boutonniere deformities

Brachial Plexus

Etiology

- common causes of brachial plexus injury: complication of childbirth and trauma
- other causes of injury: compression from tumours, ectopic ribs

Common Palsies

Table 15. Named Neonatal Palsies of the Brachial Plexus

Palsy	Location of Injury	Mechanism of Injury	Features
Duchenne-Erb Palsy	Upper brachial plexus (C5-C6)	Head/shoulder distraction (e.g. motorcycle)	Waiter's tip deformity (shoulder internal rotation, elbow extension, wrist flexion)
Klumpke's Palsy	Lower brachial plexus (C7-T1)	Traction on abducted arm	May include Horner's syndrome ("claw hand")

Differential Diagnosis

- trauma (blunt, penetrating)
- thoracic outlet syndrome
 - neurogenic – associated with cervical rib; compression of C8/T1
 - vascular – pain or sensory symptoms without cervical rib; cessation of radial pulse with provocative maneuvers
- tumour
 - schwannoma – well-defined margins makes it easier for total resection
 - neurofibromas – associated with neurofibromatosis type I (NF-1)
 - other – e.g. Pancoast's syndrome (apical lung tumour)
- neuropathy (compressive, post-irradiation, viral, diabetic, idiopathic)

Investigations

- EMG
- MRI – gold standard for identifying soft tissue masses
- CT myelogram – better than MRI for identification of nerve root avulsion and identification of pseudomeningocele. Important for preoperative identification of patients likely to require neurotisation procedures (esp. for patients with blunt trauma)

Management

Table 16. Management of Brachial Plexus Injuries

	Type	Treatment
Non-Penetrating Trauma	Concussive/compressive	Usually improves (unless expanding mass, e.g. hematoma)
	Traction/stretch	If no continued insult, follow for 3-4 months for improvement
	Obstetric palsy	Surgery if no significant improvement and/or residual paresis at 6 months of age
Penetrating Trauma	Sharp or vascular injury	Explore immediately in OR



Craniofacial Injuries

- low velocity vs. high velocity injuries determine degree of damage
- fractures cause bruising, swelling and tenderness → loss of function
- frequency: nasal > zygomatic > mandibular > maxillary
- management: can wait 5-10 days for swelling to decrease before ORIF required

Approach to Facial Injuries

- ATLS protocol
- inspect, palpate, clinical assessment for injury to underlying structures (e.g. facial nerve)
- visual assessment
- tetanus prophylaxis
- radiological evaluation
- wound irrigation with NS/RL and remove foreign materials
- conservative debridement of detached or nonviable tissue
- repair when patient's general condition allows (soft tissue injury: <8 h preferable)

Investigations (see Table 17)

- CT:
 - Axial and Coronal (specifically request 1.5 mm cuts) – for fractures of upper and middle face (not good for mandible)
 - indicated for high velocity trauma, complex facial fractures, orbital floor, panface fractures, pre-op assessment
- panorex radiograph – shows entire upper and lower jaw; best for isolated mandible fracture as patient must be able to sit

Table 17. Imaging of the Craniofacial Skeleton

Structure	Appropriate Imaging
Mandible	Panoramic (panorex)* CT
Zygomatic and orbital bones	CT scan* Water's view (occipitomeatal, A-P "from below"), Town's, AP
Nasal bones	No x-ray required – clinical
Maxilla	CT scan – axial and coronal*

*Best imaging method

Treatment

- consultation when indicated (dentistry, ophthalmology)
- re-establish normal occlusion
- pursue normal eye function
- restore stability of face and appearance

Complications

- diplopia/enophthalmos/blindness
- intracranial pathology such as cerebrospinal fluid (CSF) leak, bleeding and SIADH
- sinusitis
- functional abnormalities (i.e. malocclusion)
- infection – extremely rare
- poor cosmesis; need for 2° surgery

Mandibular Fractures

- always two points of injury since it is a ring structure (includes fractures and dislocations)
- commonly at sites of weakness (condylar neck, angle of mandible, region of 3rd molar or canine tooth)

Etiology

- anterior force: bilateral fractures
- lateral force: ipsilateral subcondylar and contralateral angle or body fracture
- note: classified as open if fracture into tooth bearing area (alveolus)

Clinical Features

- pain, swelling, difficulty opening mouth ("trismus")
- malocclusion, asymmetry of dental arch
- damaged, loose, or lost teeth
- palpable "step" along mandible
- numbness in V3 distribution
- intra-oral lacerations or hematoma (sublingual)
- chin deviating toward side of a fractured condyle



Patients with major facial injuries are at risk of developing upper airway obstruction (displaced blood clots, teeth or fracture fragments; swelling of pharynx and larynx; loss of support of hyomandibular complex → retroposition of tongue). Also at risk of ocular injury.



Suspect C-spine injury with any facial trauma. C-spine evaluation before radiographs are ordered.



Consider intracranial trauma; rule out skull fracture.



Signs of Basal Skull Fracture
 1. Battle's sign (bruised mastoid process)
 2. Hemotympanum
 3. Raccoon eyes (periorbital bruising)
 4. CSF otorrhea



Facial bone injuries with orbit involved require ophthalmology consult.

Classification

Table 18. Mandibular Fracture Classifications by Anatomic Region (refer to Figure 33)

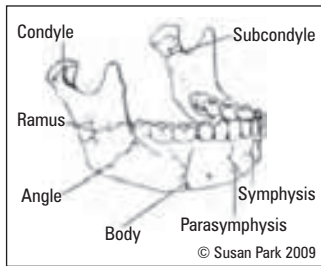


Figure 33. Mandibular Fracture

	Areas/Boundaries
Symphysis	Midline of the mandible; between the central incisors from the alveolar process through the inferior border of the mandible
Body*	From the symphysis to the distal alveolar border of the third molar
Angle	Triangular region between the anterior border of the masseter and the posterosuperior insertion of the masseter distal to the third molar
Ramus	Part of the mandible that extends posteriosuperiorly into the condylar and coronoid processes
Condylar	Area of condylar process of mandible
Subcondylar	Area below the condylar neck (i.e. sigmoid notch) of the mandible
Coronoid Process	Area of the coronoid process of mandible

*Most common mandibular fracture type

Treatment

- maxillary and mandibular arch bars wired together (intramaxillary fixation) or ORIF
- antibiotics to cover against *S. aureus* and anaerobes

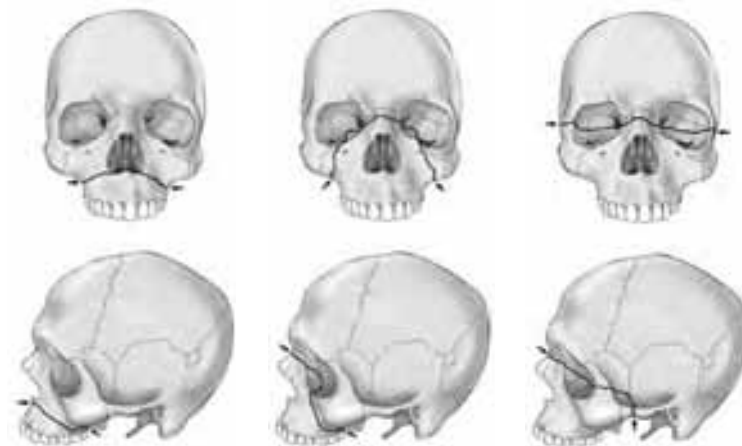
Complications

- malocclusion, malunion
- tooth loss, and possible sensation loss
- temporomandibular joint (TMJ) ankylosis

Maxillary Fractures

Table 19. Le Fort Classification

	Le Fort I	Le Fort II	Le Fort III
Alternative Name	Guerin fracture	Pyramidal fracture	Craniofacial dysjunction
Type of fracture	Horizontal	Pyramidal	Transverse
Structures involved	Piriform aperture Maxillary sinus Pterygoid plates	Nasal bones Medial orbital wall Maxilla Pterygoid plates	Nasofrontal suture Zygomatofrontal suture Zygomatic arch Pterygoid plates
Anatomical result	Maxilla divided into 2 segments	Maxillary teeth separated from face	Detach entire midfacial skeleton from cranial base



Le Fort I Fractures

Le Fort II Fractures

Le Fort III Fractures

© Rio Sakay 2007

Nasal Fractures

Etiology

- lateral force → more common, good prognosis
- anterior force → can produce more serious injuries
- most common facial fracture

Clinical Features

- epistaxis/hemorrhage, deviation/flattening of nose, swelling, periorbital ecchymosis, tenderness over nasal dorsum, crepitus, septal hematoma, respiratory obstruction, subconjunctival hemorrhage
- depression and splaying of nasal bones causing a saddle deformity
- important to clinically assess for naso-orbital-ethmoid (NOE) fractures

Treatment

- nothing
- always drain **septal hematomas** as this is a cause of septal necrosis with perforation (saddle nose deformity)
- closed reduction with Asch or Walsham forceps under anesthesia, pack nostrils with Adaptic®, nasal splint for 7 days
- best reduction immediately (<6 hours) or when swelling subsides (5-7 days)
- rhinoplasty may be necessary later for residual deformity (30%)

Naso-orbital Ethmoid (NOE) Fractures

Etiology

- fractures of the nasal and ethmoid bones of the medial orbit
- problematic and may lead to greatest change in facial appearance
- Markowitz-Manson classification:
 - Type 1: Single, central fragment, medial canthal ligament intact
 - Type 2: Comminuted central fragment, medial canthal ligament intact
 - Type 3: Severe comminution of central fragment and disrupted medial canthal ligament

Clinical Presentation

- telecanthus (increased intercanthal distance secondary to medial canthal ligament disruption)
- orbital rim step-off
- similar to nasal fractures (see above)

Treatment

- surgical repair to restore intercanthal distance, nasal projection and orbital anatomy

Zygomatic Fractures

- 3 categories (see Figure 34)
 1. fracture restricted to zygomatic arch
 2. depressed fracture of zygomatic complex (zygoma)
 3. unstable fracture of zygomatic complex (tetrapod fracture) – separations occur at maxilla, frontal bone, temporal bone and orbital rim

Clinical Features

- flattening of malar prominence (view from above)
- pain over fractures on palpation
- numbness in V2 distribution (infraorbital and superior dental nerves)
- palpable step deformity in bony orbital rim (especially inferiorly)
- often associated with fractures of the orbital floor
- ipsilateral epistaxis; trismus (lock jaw)

Treatment

- if undisplaced, stable and no symptoms, then soft diet; no treatment necessary
- ophthalmologic evaluation if suspected orbital injury
- uncomplicated zygomatic arch fractures can be elevated using Gillies approach: leverage on the anterior part of the zygomatic arch via a temporal incision; stabilization often unnecessary
- ORIF for displaced or unstable fractures of zygomatic complex

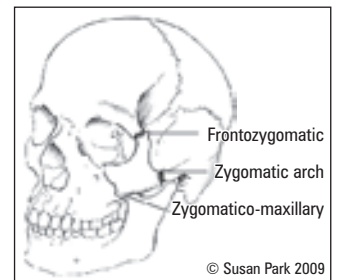


Figure 34. Zygomatic Fractures

Orbital Floor Fractures

- see Ophthalmology, OP43

Definition

- fracture of floor of orbit \pm intact infraorbital rim (see Figure 35)
- may be associated with nasoethmoid fracture

Etiology

- blunt force to eyeball \rightarrow sudden increase in intra-orbital pressure (e.g. baseball or fist)

Clinical Features

- **check visual fields and acuity for injury to globe**
- periorbital edema and bruising, subconjunctival hemorrhage
- ptosis, exophthalmos, exorbitism, or enophthalmos
- orbital rim step-offs with possible infraorbital nerve anesthesia
- vertical dystopia (abnormal displacement of the entire orbital cone in the vertical plane); diplopia looking up or down (entrapment of inferior rectus), limited EOM
- orbital entrapment:
 - clinical diagnosis that is a surgical emergency
 - diplopia with vertical gaze; limited EOM
 - severe pain or nausea and vomiting with eye movement
 - requires urgent ophthalmology evaluation and surgical repair

Investigations

- CT (diagnostic) – axial and coronal views
- diagnostic manoeuvre for entrapment is **Forced Duction** test (pulling on inferior rectus muscle with forceps to ensure full ROM) under anesthesia

Treatment

- surgical repair indicated if: urgent repair for entrapment, floor defect > 1 cm, any size defect with enophthalmos or persistent diplopia (>10 days)
- reconstruction of orbital floor with bone graft or alloplastic material
- ophthalmologic evaluation suggested

Complications

- persistent diplopia
- enophthalmos

Superior Orbital Fissure (SOF) Syndrome

- fracture of SOF causing ptosis, proptosis, anesthesia in V1 distribution, and painful ophthalmoplegia (paralysis of CN III, IV, VI)
- uncommon complication seen in Le Fort II and III fractures (1/130)
- recovery time reported as 4.8-23 weeks following operative reduction of fractures

Orbital Apex Syndrome

- fracture through optic canal with involvement of CN II at apex of orbit
- symptoms are the same as SOF syndrome plus vision loss
- treatment is urgent decompression of fracture in optic canal or steroids (emergency)

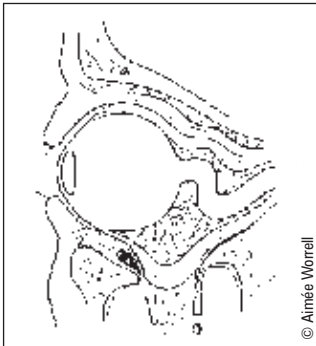


Figure 35. Blow-Out Fracture



Diplopia can present late in orbital blow-out fractures.

Breast Surgery

Breast Reconstruction

- integral part of breast cancer treatment
- two basic methods: implants (1 stage or 2 stage) or autologous tissue (see Table 20)
- may also require breast balancing procedure and nipple areola reconstruction

Pre-Reconstruction Considerations

- radiation: treatment before and after mastectomy is a relative contraindication to alloplastic reconstruction
- recipient tissue: skin sparing mastectomy allows for the use of implants without tissue expanders (1 stage process)
- donor tissue: limited availability of suitable donor tissue (lack of tissue, scar, previous surgery that interferes with blood supply) may prevent the use of autologous tissue reconstruction
- timing (immediate vs. delayed)
- contralateral breast: may not be possible to reconstruct a breast of the same size or shape as the contralateral breast. Breast reduction or mastopexy may be considered in opposite breast (see Table 21)
- other considerations: patient's age and co-morbidities, prognosis, body weight, characteristics of chest wall and patient's attitude



Patients may require a balancing procedure on contralateral side.

Table 20. Options for Breast Reconstruction

Procedure	Definition	Surgical Details	Other Comments
Implant	Use of synthetic material (silicone or saline implants)	<p><i>With expanders (2 Stages):</i> Use tissue expanders before replacement with implants to help facilitate breast ptosis. (see further discussion on Tissue Expanders below)</p> <p><i>Without expanders (1 Stage):</i> In skin-sparing mastectomy, enough skin is available for immediate placement of implant</p> <p>Reconstruction with implants requires a submuscular placement of devices</p>	Complications: capsular contraction (foreign body reaction to implants), rupture or leakage of implant, increased risk of infection, 35% revision rate over 5 years
Autologous Tissue	Use of patient's own tissue	Many flap options: DIEP (deep inferior epigastric perforator), TRAM (transverse rectus abdominus), Latissimus dorsi, SIEA (superficial inferior epigastric artery), SGAP (superior gluteal artery perforator), and IGAP (inferior gluteal artery perforator)	Offers reduced long-term morbidity and natural consistency
Nipple Areola Reconstruction	Final stage of breast reconstruction	<p>Usually require tattooing for areola reconstruction</p> <p>Local vs. distant flap/graft:</p> <ol style="list-style-type: none"> 1. Local: fish tail or skate flap most common; these flaps allow simultaneous nipple and areola reconstruction 2. Distant: opposite nipple, earlobe, abdominal skin, costal cartilage, labia 	Usually performed 3 months post-reconstruction

Breast Tissue Expanders

- types: textured vs. smooth, both with integrated port
- placement: sub-pectoral, total submuscular (pectoral/serratus)
- size: depends on contralateral breast and desired size
 - generally over-expanded to facilitate ptosis
- timing of expansion: begins when wound fully healed (usually 2 weeks post-op), and implants are expanded weekly or bi-weekly until complete (up to 3 months). Expanders are exchanged for implants after another 3 months for consolidation of expanded skin

Aesthetic Surgery

Aesthetic Procedures

Table 21. Aesthetic Procedures

Location	Procedure	Description
Head/Neck	Hair transplants	Aesthetic improvement of hair growth patterns using grafts of flaps
	Otoplasty	Surgical correction of protruding ears
	Brow lift	Surgical procedure to lift low brows
Face	Rhytidectomy	Surgical procedure to reduce wrinkling and sagging of the face and neck. "Face lift"
	Blepharoplasty	Surgical procedure to shape or modify the appearance of eyelids by removing excess eyelid skin ± fat pads
	Rhinoplasty	Intranasal surgical reconstruction of the nose
	Genioplasty	Chin augmentation via osteotomy or synthetic implant to improve contour
	Lip augmentation	Procedure to create fuller lips and to reduce wrinkles around the mouth using collagen injections, fat transferred from other body parts, or implantable materials
Skin	Chemical peel	Application of one or more exfoliating agents to the skin resulting in destruction of portions of the epidermis and/or dermis with subsequent tissue regeneration
	Dermabrasion	Skin re-surfacing by sanding with a rapidly rotating abrasive tool. Often used to reduce scars, irregular skin surfaces and fine lines
	Laser resurfacing	Application of laser to the skin which ultimately results in collagen reconfiguration and subsequent skin shrinking and tightening. Often used to reduce scars and wrinkles
	Injectable fillers	An injectable substance is used to decrease frown lines, wrinkles and nasolabial folds Substances include collagen, fat, hyaluronic acid and calcium hydroxyapatite
Other	Abdominoplasty	Removal of excess skin and repair of rectus muscle laxity (rectus diastasis). "Tummy tuck"
	Breast augmentation	Surgical breast enhancement with silicone or saline implants (see Figure 36)
	Calf augmentation	Augmentation of calf muscle with implants
	Liposuction	Surgical removal of adipose tissue for body contouring (not a weight loss procedure)
	Mastopexy	Surgical breast lift to elevate breast mound and tighten the skin envelope in ptotic breasts
	Breast reduction	Surgical breast reduction for relief of physical symptoms
	Sclerotherapy	Injection with a sclerosant to treat telangiectasias and varicose veins

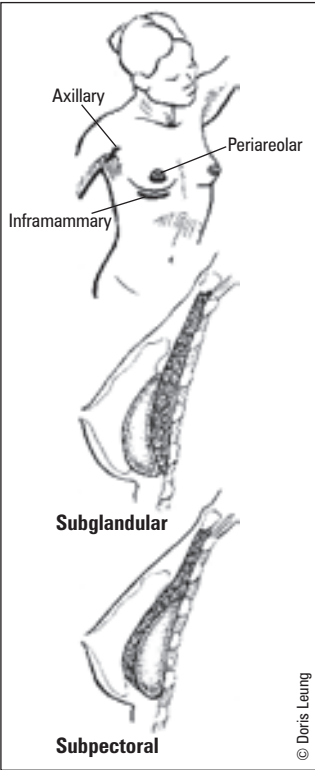


Figure 36. Augmentation Mammoplasty: Incision Lines and Implant Placement

Pediatric Plastic Surgery

Craniofacial Anomalies

Table 22. Pediatric Craniofacial Anomalies

	Definition	Epidemiology	Clinical Features	Treatment
Cleft Lip	Failure of fusion of maxillary and medial nasal processes M:F = 2:1	1 in 1000 live births (1 in 800 Caucasians, increased in Asians, decreased in Blacks) More common on the left (cleft of left lip/palate in boys has hereditary component)	Classified as incomplete/complete and uni/bilateral 2/3 cases: unilateral, left sided, male	Cleft lip team; Surgery (3 months): Millard or Tennison-Randall; corrections usually required later on (esp. for nasal deformity)
Cleft Palate	Failure of fusion of lateral palatine/median palatine processes and nasal septum	Isolated Cleft Palate: 0.5 per 1000 (no racial variation) F > M	Classified as incomplete/complete and uni/bilateral Isolated (common in females) or in conjunction with cleft lip (common in males)	Special bottles for feeding Speech pathologist Surgery (6-9 months): Von Langenbeck or Furlow Z-Plasty ENT consult – often recurrent OM, requiring myringotomy tubes
Craniosynostosis	Premature fusion of 1+ cranial sutures Primary – abnormal suture, no known cause This may limit brain perpendicular to the suture and cause compensatory growth parallel to the fused suture	1 in 2000 live newborns; M:F = 52:48 Syndromic includes: Crouzon's, Apert's, Saethre-Chotzen, Carpenter's, Pfeiffer's Jackson-Weiss and Boston-type syndromes	Syndromic – assoc. with genetic mutation Secondary (to microcephaly, hyperthyroid, rickets, etc.) Dx: irregular head shape, craniofacial abnormalities, x-ray	Multidisc. team (incl. neurosurg, ENT, genetics, dentistry, peds, SLP) Early surgery prevents secondary deformities ↑ ICP is an indication for emergent surgery ICU bed may be req'd post-surgically

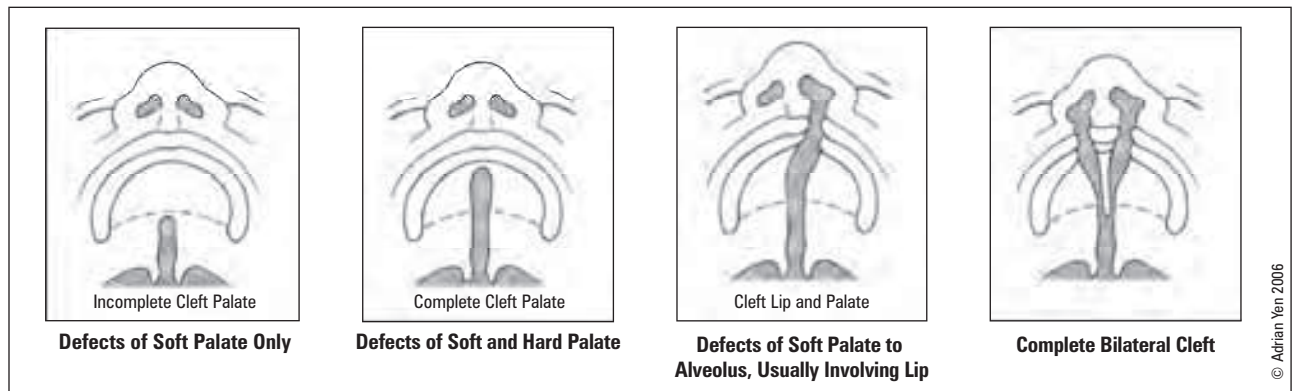


Figure 37. Types of Cleft Lips and Palates

Congenital Hand Anomalies

Table 23. American Society for Surgery of the Hand (ASSH) Classification of Congenital Hand Anomalies

Classification	Example	Features	Treatment
A. Failure of formation	Transverse Absence (congenital amputation)	At any level (often below elbow/wrist)	Early prosthesis
	Longitudinal Absence (phocomelia)	Absent humerus Thalidomide-assoc.	
	Radial Deficiency (radial club hand)	Radial deviation Thumb hypoplasia M > F	Physio + splinting Soft tissue release if splinting fails Distraction osteogenesis (Ilizarov) ± wedge osteotomy Tendon transfer Pollicization
	Thumb Hypoplasia	Degree ranges from small thumb with all components to complete absence	Depends on degree – may involve no treatment, webspace deepening, tendon transfer, or pollicization of index finger
	Ulnar Club Hand	Rare, compared to radial club hand Stable wrist	Splinting and soft-tissue stretching therapies Soft-tissue release (if above fails) Correction of angulation (Ilizarov distraction)
	Cleft Hand	Autosomal dominant Often functionally normal (depending on degree)	First web space syndactyly release Osteotomy/tendon transfer of thumb (if hypoplastic)
B. Failure of differentiation/separation	Syndactyly	Fusion of 2+ digits 1/3000 live births M:F = 2:1 Classified as partial/complete Simple (skin only) vs. complex (osseous or cartilaginous bridges)	Surgical separation before 6-12 months of age Usually good result
	Symbrachydactyly	Short fingers with short nails at fingertips	Digital separation (more difficult) Webspace deepening
	Camptodactyly	Congenital flexion contracture (usually at PIP, esp. 5th digit)	Early splinting Volar release Arthroplasty (rarely)
	Clinodactyly	Radial or ulnar deviation Often middle phalanx	None (usually). If severe, osteotomy with grafting
C. Duplication	Polydactyly	Congenital duplication of digits May be radial (increased in Aborigines and Asians) or central or ulnar (increased in Blacks)	Amputation of least functional digit Usually > 1 yr of age (when functional status can be assessed)
D. Overgrowth	Macroductyly	Rare	None (if mild) Soft tissue/bony reduction
E. Undergrowth	Brachydactyly	Short phalanges	Removal of non-functional stumps Osteotomies/tendon transfers Distraction osteogenesis Phalangeal/free toe transfer
	Symbrachydactyly (Brachysyndactyly)	Short webbed fingers	As above + syndactyly release
F. Constriction band syndrome	AKA amniotic (annular) band syndrome	Variety of presentations	Urgent release for acute, progressive edema distal to band in newborn Other reconstruction is case-specific
G. Generalized skeletal abnormality	Achondroplasia, Marfan's, Madelung's	Variety of presentations	Treatment depends on etiology

References

General Plastic Surgery Concepts

- Brown DL, Borschel GH. Michigan manual of plastic surgery. Philadelphia: Saunders, 2004.
- Daver BM, Antia NH, Furnas DW. Handbook of plastic surgery for the general surgeon second edition. New Delhi: Oxford University Press, 1995.
- Georgiade GS, Riefkohl R, Levin LS. Georgiade plastic, maxillofacial and reconstructive surgery third edition. Baltimore: Williams and Wilkins, 1997.
- Hunt TK. Wound Healing. In: Doherty GM, Way LW, eds. Current surgical diagnosis & treatment twelfth edition. Norwalk, CT: McGraw-Hill, 2006.
- Janis JE. Essentials of Plastic Surgery: A UT Southwestern Medical Center Handbook. St. Louis, MO: Quality Medical, 2007.
- Noble J. Textbook of primary care medicine third edition. St. Louis: Mosby Inc, 2001.
- Ong YS, Samuel M and Song C. Meta-analysis of early excision of burns. Burns. 2006; 32: 145-50.
- Plastic Surgery Educational Foundation. Plastic and reconstructive surgery essentials for students. Arlington Heights, IL: Plastic Surgery Educational Foundation, 2007. http://www.plasticsurgery.org/medical_professionals/publications/Essentials-for-Students.cfm.
- Richards AM. Key notes in plastic surgery. Great Britain: Blackwell Science Ltd, 2002.
- Sermer NB. Practical plastic surgery for non-surgeons. Philadelphia: Hanley & Belfus Inc, 2001.
- Smith DJ, Brown AS, Cruse CW et al. Plastic and reconstructive surgery. Chicago: Plastic Surgery Educational Foundation, 1987.
- Stone C. Plastic surgery: facts. London: Greenwich Medical Media Ltd, 2001.
- Townsend CM. Sabiston textbook of surgery – the biological basis of modern surgical practice sixteenth edition. Philadelphia: W.B. Saunders Company, 2001.
- Vasconez HC, Ferguson REH, Vasconez LO. Plastic & reconstructive surgery. In: Doherty GM, Way LW, eds. Current surgical diagnosis & treatment twelfth edition. Norwalk, CT: McGraw-Hill, 2006.
- Weinzwieg J. Plastic surgery secrets. Philadelphia: Hanley and Belfus Inc, 1999.

Hand

- American Society for Surgery of the Hand. The hand: examination and diagnosis third edition. Philadelphia: Churchill-Livingston, 1990.
- Beredjicklian PK, Bozenika DJ. Review of hand surgery. Philadelphia: Saunders, 2004.
- Graham B, Regehr G, Naglie G, Wright J. Development and validation of diagnostic criteria for carpal tunnel syndrome. J Hand Surg 2006; 31(6): 919.e1-919.e7.

Notes

Daniel Rosenfield and Susanna Zachara, chapter editors
 Christopher Kitamura and Michelle Lam, associate editors
 Janine Hutson, EBM editor
 Dr. Ian Johnson and Dr. Fran Scott, staff editors

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Historical Context of Public Health

Definitions

• Population Health

- health of the population as measured by health status indicators (e.g. life expectancy, low birth weight rates)
- influenced by: physical, biological, social, environmental, and economic factors; personal health behaviours; health care services
- refers to the prevailing or desired level of health in the population of a specific country/region/subset of population

• Public Health

- systematic societal efforts to protect, promote, and restore the health of the public
- refers to the practices, procedures, institutions, and disciplines required to achieve the desired state of population health

• Community Medicine

- the postgraduate study of health and disease in the population or a specified community
- goal: to identify and address health problems and evaluate the extent to which health services and others address these issues

Source: Last JM. *A Dictionary of Epidemiology*, 4th ed. Oxford University Press. 2001.

Historical Perspective

Public health has evolved through three main epidemiological phases:

1. Infectious diseases

- examples from this era: smallpox, plagues, and tuberculosis
- most illnesses (e.g. malaria) are successfully treated in the developed world but still remain an issue in some developing countries
- recent notable successes: eradication of smallpox and near eradication of polio

2. Chronic diseases

- examples from this era: heart disease and cancer
- progression of chronic disease results in the most common causes of death and disability due to:
 - ♦ changes in lifestyle (e.g. increased prevalence of smoking and sedentary lifestyle)
 - ♦ reduction in infectious disease mortality resulting in increased life span and therefore prevalence of chronic diseases
 - ♦ exposure to other factors (e.g. asbestos) leading to cancer
 - ♦ increasing urbanization and changes in social structure

3. Re-emerging infectious diseases

- examples from this era: AIDS, hantavirus, and drug-resistant tuberculosis, H1N1
- this new era has emerged due to:
 - ♦ encroachment on natural environments and contact with unfamiliar pathogens (e.g. HIV)
 - ♦ fast international travel facilitating the rapid spread of organisms
 - ♦ inefficient and inappropriate use of antibiotics leading to drug-resistant organisms (e.g. drug resistant TB, MRSA, VRE)
 - ♦ global warming, possibly increasing the size of regions at high risk for transmission of vector-borne diseases (e.g. malaria and dengue, west Nile virus)

Public Health Services in Canada

Mission: to promote and protect the health of Canadians through leadership, partnership, innovation and action in public health

- local public health units and services within regional health authorities provide programs and activities for health protection, promotion, and disease prevention at local and regional levels
- catchment-area populations range from hundreds to thousands of people, covering areas of 15 to 1.5 million km²

For the LMCC exam, it is recommended that you read all of Chapter 15 in Shah CP. *Public Health and Preventative Medicine in Canada*. 5th edition. Elsevier Canada. 2003.



Five Core Functions for All Public Health Units

1. Population health assessment
2. Health surveillance
3. Health promotion
4. Disease and injury prevention
5. Health protection

Legislation and Public Health in Canada

Federal

- 3 divisions of the federal government are responsible for public health:
 - Health Canada
 - ♦ responsible for helping Canadians maintain and improve their health, while respecting individual choices and circumstances
 - ♦ provides health services to First Nations, Aboriginal peoples, and those in the Canadian military
 - ♦ approves new drugs and medical devices
 - ♦ liaises with other national health organizations (e.g. WHO)
 - Canadian Food Inspection Agency
 - ♦ monitors genetically modified foods
 - ♦ monitors food importation
 - ♦ deals with animal-related infections (e.g. BSE)
 - Public Health Agency of Canada
 - ♦ an independent body created to strengthen public health capacity, but reports to federal government via the Chief Public Health Officer
 - ♦ created to deliver the federal government's commitment to protect the health and safety of Canadians
 - ♦ focuses on preventing chronic diseases, preventing injuries, and responding to public health emergencies and infectious disease outbreaks
 - ♦ oversees immigration screening, protects Canadian borders (e.g. airport health inspection)

Provincial

- legislation is in the form of Acts and Regulations
- each province has its own *Public Health Act* or equivalent. In Ontario, it is the *Health Promotion and Protection Act*
 - designates the creation of local health units or geographic areas for the provision of public health services
 - gives powers to the Chief Medical Officer of Health to control public health hazards
 - specifies infectious diseases to be reported to public health units by physicians, laboratories and hospitals (see *Appendix 1*)
 - has the ability to mandate programs that address public health issues, i.e. injury prevention programs, infectious disease control programs, environmental health (e.g. safe food and water) and chronic disease prevention

Municipal

- local boards of health deliver programs mandated by provincial legislation in accordance with local needs
- boards of health can be connected directly with regional governments, or can be autonomous with municipal representation
- boards of health are responsible for the delivery of most public health services, such as:
 - infectious disease control, including the follow-up of reported diseases and management of outbreaks
 - inspection of food premises including those in hospitals, nursing homes, and restaurants
 - family health services including pre-conception, preschool, school-aged, and adult health programs
 - tobacco control legislation enforcement
 - assessment and management of local environmental health risks
 - collection and dissemination of local health status reports
 - some public dental health services to children
- by-laws may be legislated by municipal government to facilitate public health issues (e.g. anti-idling to reduce air pollution)

Medical Officer of Health

- appointed to each public health unit by the board of health
- boards of health are composed of individuals appointed by the municipality and the province
- full-time position that can only be held by a licensed physician with public health training
- physicians can also be appointed as Associate Medical Officers of Health
- responsibilities of the Medical Officer of Health include:
 - reporting to the board of health on matters of public health
 - supervision of community sanitation, including food premises and places of lodging
 - control of infectious and reportable diseases, including immunization
 - implementation of disease and injury prevention, as well as health promotion and protection programs as needed
 - collection and analysis of epidemiological data
 - occupational and environmental health surveillance

- implementation of health programs, including:
 - ♦ counseling
 - ♦ family planning services
 - ♦ parenting programs, prenatal courses
 - ♦ preschool and school health services
 - ♦ disease screening programs to reduce morbidity and mortality
 - ♦ tobacco use prevention programs
 - ♦ nutrition services to schools and seniors' centres
- the Medical Officer of Health can require an individual to take or refrain from any action due to a public health hazard including an order to:
 - ♦ vacate premises or close a business
 - ♦ update or maintain a business or home with maintenance work
 - ♦ receive treatment by a physician if infected (for specified diseases only)
 - ♦ give a blood sample
- the Medical Officer of Health can also
 - ♦ investigate and manage health hazards
 - ♦ order the isolation or quarantine of individuals who have or may have specified communicable diseases

Determinants of Health

Concepts of Health

- **Disease:** abnormal, medically-defined changes in the structure or function of the human body
- **Illness:** an individual's experience or subjective perception of a lack of physical or mental well-being and consequent inability to function normally in social roles
- **Impairment:** any loss or abnormality of psychological, physiological, or anatomical structure or function
- **Disability:** any restriction or lack of ability to perform an activity within the range considered normal for a human being
- **Handicap:** the disadvantage for an individual arising due to impairment and disability
 - limits or prevents the fulfilment of an individual's normal role as determined by society and depends on age, sex, social, and cultural factors
 - changes the individual's relationship with the physical and social environment
- **Sick Role:** in addition to being physically sick, an individual may adopt a role that is defined by society as 'sick'
 - may allow the individual to be exempt from work and prior obligations, provided they adhere to certain conditions such as trying to ameliorate their health status and are seeking appropriate medical care
- **Culture:** plays a key role in health and illness – often impacts how individuals present and cope with their illnesses, i.e. certain cultural groups remain stoic in the face of tremendous illness; whereas others may be more prone to seek medical attention



Definitions of Health

- First multidimensional definition of health, as defined by the World Health Organization (WHO) in 1948: "A complete state of physical, mental and social well being and not merely the absence of illness"
- WHO updated the definition (socioecological definition) of health in 1986: "The ability to identify and to realize aspirations, to satisfy needs, and to change or cope with the environment. Health is therefore a resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities."



Determinants of Health

1. Income and social status
2. Social support networks
3. Education and literacy
4. Employment and working conditions
5. Social environment
6. Physical environment
7. Personal health practices and coping skills
8. Healthy child development
9. Biology and genetic endowment
10. Health services
11. Gender
12. Culture

Source: Public Health Agency of Canada

Determinants of Health

- 1974: Marc Lalonde, Minister of Health, presented the health field concept entitled *A New Perspective on the Health of Canadians* which included four elements that interact to determine health: **human biology, environment, lifestyle, and the health care organization**
- since then this concept has been expanded to include numerous determinants of health (see below)

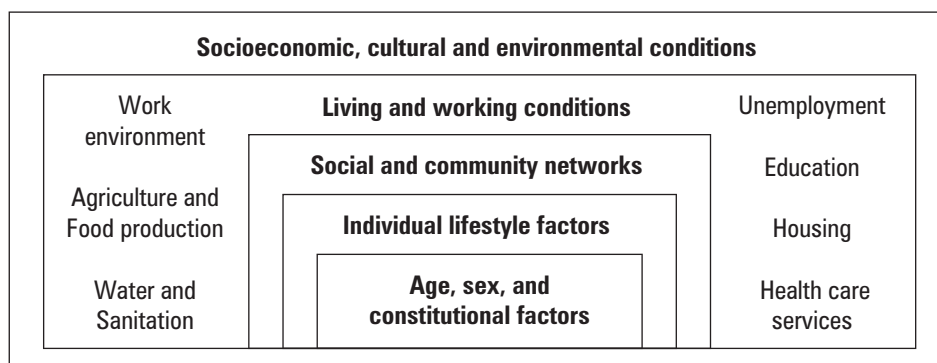


Figure 1. Determinants of Health Model

Adapted from Dahlgren G, Whitehead M. *Policies and strategies to promote social equity in health*. Stockholm: Institute of Future Studies, 1991.

Vulnerable Populations

Table 1. Health Determinants of Vulnerable Populations

	Psychosocial/Socioeconomic	Physical Environment	Lifestyle and Behaviour
Aboriginal Peoples	Low income Family violence Low education status Unemployment Homelessness	Crowded housing Inefficient ventilation Environmental toxins	Smoking Substance abuse Excessive gambling Poor nutrition Sedentary lifestyle High BMI High risk behaviours
Seniors	Elder abuse Lack of emotional support	Low hazard tolerance Institutionalization	Inactivity Polypharmacy Medical co-morbidities
Children in Poverty	Low income Family dysfunction Lack of educational opportunities	Housing availability Unsafe housing Lack of recreational space	Poor supervision Food insecurity High risk behaviours
People with Disabilities	Low income Low education status Discrimination	Institutionalization (7%) Barriers to access Transportation challenges	Substance abuse Poor nutrition Inactivity Dependency for ADLs
New Immigrants	Access to community services Cultural perspectives	Diseases and conditions in country of origin (e.g. smoke from wood fires, incidence of TB, etc.)	
Homeless Persons	Low income Mental illness	Exposure to temperature extremes	Substance abuse Violence

Note: this chart delineates the major challenges faced by each group, but the issues listed are not unique to each population

Disease Prevention

Disease Prevention Strategies

- measures aimed at preventing, interrupting, or slowing the progression of disease

Primary Prevention

- implemented to prevent disease from occurring
- immunization programs exist in most countries to address 6 major causes of pediatric morbidity and mortality that are preventable by vaccines, e.g.:
 - measles
 - diphtheria
 - pertussis
 - tetanus
 - polio
 - tuberculosis (not routine in Canada or the U.S.)
- additional immunizations are offered in Canada depending on jurisdiction: mumps, rubella, hepatitis B, *Haemophilus influenzae* type B, varicella, HPV, conjugated pneumococcal and meningococcal vaccines (see [Pediatrics](#), P4)

Secondary Prevention (Screening)

- presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly
- types of screening
 - mass screening: screening all members of a population for a disease (e.g. phenylketonuria (PKU) and hypothyroidism in newborns)
 - selective screening: screening of a specific subgroup of the population at risk for a disease (e.g. mammography in women >50 years old)
 - multiphasic screening: the use of many measurements and investigations to look for many disease entities (e.g. periodic health exam)
- ideal criteria for screening tests
 - disease
 - must cause significant suffering and/or death
 - natural history must be understood
 - must have an asymptomatic stage that can be detected by a test
 - early detection and intervention must result in favourable outcomes
 - incidence is not too high or too low
 - test
 - high specificity and sensitivity
 - safe, rapid, easy, relatively inexpensive
 - acceptable to providers and population



Example of Primary Prevention: Gardasil Vaccine and Its Efficacy in the Prevention of Cervical Cancer

Gardasil® is a quadrivalent HPV vaccine covering strains 6,11,16,18. The efficacy of Gardasil® was studied in 4 randomized, double-blind, placebo controlled trials on females between 16 and 26 years of age and was found to prevent nearly 100% of precancerous cervical changes for up to 4 years after vaccination.



Disease Prevention Strategies

- Primary: before disease occurs, e.g. immunizations, seatbelt use, smoking cessation programs for lung cancer prevention
- Secondary: early detection of disease, e.g. mammography, routine Pap smears
- Tertiary: treatment and rehabilitation of existing disease, e.g. ACEI for hypertension
- Passive prevention: measures that operate without the person's active involvement, e.g. airbags in cars
- Active prevention: measures that a person must do on their own, e.g. wearing a seatbelt

- healthcare system
 - ♦ adequate capacity for reporting, follow-up, and treatment of positive screens
 - ♦ cost effective
 - ♦ sustainable program
 - ♦ clear policy guidelines

Tertiary Prevention

- treatment and rehabilitation of disease after it has been diagnosed so as to prevent progression and permanent disability (e.g. HbA1c, eye, and foot monitoring for diabetes)

Health Promotion Strategies

Table 2. Disease Prevention versus Health Promotion Approach

Disease Prevention	Health Promotion
Health = absence of disease	Health = positive and multidimensional concept
Medical model (passive role)	Participatory model of health
Aimed mainly at high-risk groups in the population	Aimed at the population in its total environment
Concerns a specific pathology	Concerns a network of issues
One-shot strategy	Diverse and complementary strategies
Directive and persuasive strategies	Facilitating and enabling approaches
Directive measures enforced in target groups	Incentive measures offered to the population
Focused mostly on individuals and groups of subjects	Focused on a person's health status and environment
Preventive programs considered the affairs of professional groups from health disciplines	Non-professional organizations, civic groups, local, municipal, regional, and national governments necessary for achieving the goal of health promotion

Source: Shah CP. *Public Health and Preventive Medicine in Canada*. 5th ed. Elsevier Canada. 2003.

Ottawa Charter for Health Promotion (1986)

- **health promotion:** the process of enabling people to increase control over and to improve their health
- the charter states that governments and health care providers should be involved in a **health promotion process** that includes
 1. building healthy **public policy**
 2. creating supportive **environments**
 3. strengthening **community action**
 4. developing **personal skills**
 5. re-orienting **health services**

Jakarta Declaration on Health Promotion into the 21st Century (WHO 1997)

- reiterated the commitment of health promotion
- first of the health promotion conferences to involve the private sector
- formally cited poverty as the greatest threat to health
- priorities for health promotion:
 - promote social responsibility for health
 - increase investments for health development
 - consolidate and expand partnerships for health
 - increase community capacity and empower the individual
 - secure an infrastructure for health promotion

Healthy Public Policy

- characterized by an explicit concern for health and equity in all areas of policy and by an accountability for health impact
- main aim: to create a supportive environment to enable people to lead healthy lives, thereby making healthy choices easier for citizens
- government sectors must take into account health as an essential factor when formulating policy and should be accountable for health consequences of their policy decisions

1. Fiscal

- tax and pricing policies established to impose additional costs to undertake “unhealthy” behaviours (e.g. taxes on tobacco and alcohol)

2. Legislative

- implementation of legal deterrents to individual behaviours (e.g. anti-smoking bylaws, seat belt legislation, bicycle helmet bylaws, legal drinking age)

3. Social

- responsibility of improving health beyond providing traditional health services, the premise of universal health care under the *Canada Health Act* (e.g. providing affordable housing and ensuring adequate income)
- may improve the health of the population independently of the health care system

Source: International Conference on Health Promotion, Adelaide, South Australia (1998)



Labonte Model of Community Development

- Personal empowerment
- Small group development
- Community organization
- Coalition advocacy
- Political action

Community Development

- process of community members identifying issues and problems affecting their community and subsequently developing the skills and capacity to implement change

Community-Based Prevention

- public health service (prevention or promotion) focused on an entire community as opposed to only high-risk groups
- “community-based approaches” are population-based multifactorial initiatives that make use of community organization and social marketing to elicit change at the community level (e.g. Saskatoon's *In Motion* program)
- numerous preventable risk factors are being addressed by multiple health promotion strategies

Health Marketing

- application of the principles of commercial marketing to promote healthy changes
- involves target group analysis and segmentation of the market for specific messages and promotion strategies
- employed by both the health care system (e.g. pamphlets providing health information about HIV) and by industry (e.g. in medication advertisements)

Behaviour Change

- Health Education serves to:
 - increase knowledge and skills
 - encourage positive lifestyle changes and discourage unhealthy choices
- Health Education is an important component of eliciting behaviour change, however behaviour is not only dictated by knowledge, e.g. many smokers know smoking is bad for them but they still continue to smoke
- behaviour is a result of three factors
 1. **Predisposing factors** – knowledge, attitude, beliefs, values, intentions
 2. **Enabling factors** – skills, supports
 3. **Reinforcing factors** – health care professionals and the social context of family and community
- **Health Belief Model** (1975)
 - behaviours undertaken by individuals in order to remain healthy are a function of a set of interacting beliefs
 - beliefs include an individual's perception of his or her susceptibility to a disease, the severity of the disease, and the benefits and costs of health-related actions
 - beliefs are modified by **socio-demographic** and **psychosocial variables**
 - individuals must believe that the action will have positive consequences
 - individuals must be in a state of readiness
 - behaviour can be stimulated by cues to action, which are specific events that can encourage preventive health decisions and actions (e.g. physician recommendation, public advertising)
- **Stages of Change Model**
 - provides a framework in which the Health Belief Model is applied to facilitating behaviour change (see Figure 2), e.g. quitting smoking

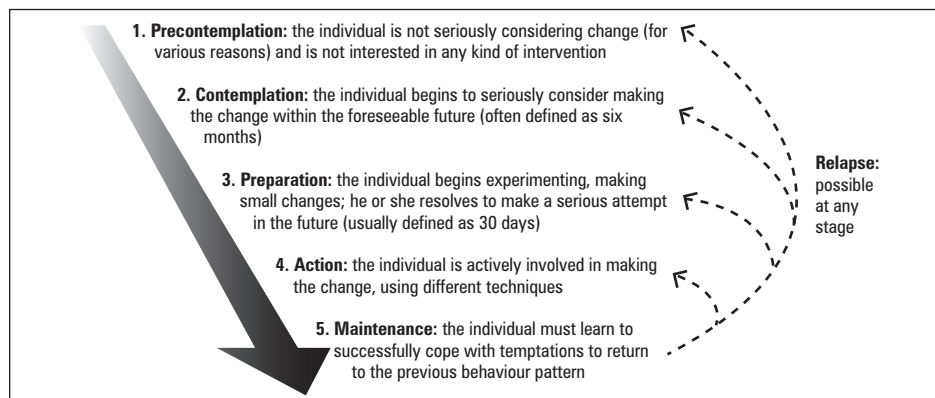


Figure 2. Stages of Change Model

Source: Prochaska JO, DeClement CC, and Norcross JC, In Search of How People Change. Applications to Addictive Behaviours. *Am Psychol* 1992; 47(9):1102-1114.

Risk Reduction Strategies

- **risk reduction:** lower the risk to health without eliminating it (e.g. avoiding sun to lower risk of skin cancer)
- **harm reduction:** tolerance of some degree of risk behaviour, while aiming to minimize the adverse outcomes associated with these behaviours (e.g. needle exchange programs)



Saskatoon's In Motion is a community-based strategy to increase physical activity through collaborative community efforts. 98% of all Saskatoon schools have now committed to meeting In Motion goals, including at least 30 minutes of daily physical activity per child. Elementary schools also report that students are active on one additional day per week compared to pre-program activity levels. In Motion is viewed as a best practice strategy and is now being implemented in communities and provinces across Canada.

Chief Public Health Officer's Report, 2009.



4 P's Influencing Health Marketing

1. **Product** = good health
2. **Price** = what a person must give up if he or she accepts the product "pursuing good health"
3. **Place** = the distribution channels used to reach the consumer (e.g. distributing pamphlets at the doctor's office)
4. **Promotion** = the way in which the product is promoted to the consumer

Example of Harm Reduction Strategy Summary of Findings from the Evaluation of a Pilot Medically Supervised Safer Injecting Facility

CMAJ 2006; 175(11):1399-1404

Background: This study discusses the outcomes among a population of illicit injection drug users (IDUs) after initiating a supervised safe injecting facility in Vancouver, September 2003. Legal exemption by the Canadian government was granted such that an evaluation of its results be conducted over a 3 year period.

Study Population: IDUs of the Vancouver area were allowed to inject previously obtained illicit drugs under the supervision of nurses and physicians. IDUs were offered addiction counseling and supports for appropriate community resources. A random sample of 670 IDUs was recruited and monitored from Dec 2003-July 2004.

Results: Characteristics of IDUs who used the safe injecting facility included age <30 years, history of public drug use, homelessness, daily heroin and/or cocaine injection, and recent history of overdose. Mean measures of public order problems were taken 6 weeks before and 12 weeks after initiation of the safer injection facility. It was found that the mean number of IDUs injecting daily in public, along with the mean number of publicly discarded syringes were reduced by approximately half.

Conclusions: Overall it has been found that the safer injecting facility in Vancouver has been successful in attracting IDUs at increased risk of HIV, overdose, and public injection of substances. This has resulted in lower incidences of public drug use, publically discarded syringes and sharing of needles. Other studies associated with this one have demonstrated that there has been no increase in the drug dealing, drug related crimes, or rates of new IDUs in the area surrounding the safer injecting facility.


Characteristics of Innovations that Influence Adaptability of the Change

- Simple
- Workable
- Reversible
- Flexible
- Advantageous
- Cost effective
- Low risk
- Compatible with value systems


Top 5 Causes of Mortality in Canada, 2005, by Sex
Female

1. Ischemic Heart Disease
2. Lung Cancer
3. Stroke
4. Non-ischemic heart disease(s)
5. Breast Cancer

Male

1. Ischemic Heart Disease
2. Lung Cancer
3. Stroke
4. COPD/ chronic lower respiratory disease
5. Diabetes Mellitus

Source: Statistics Canada. *CANSIM*, 2005. Table 102-0552 and Catalogue No.84F5029X.


Top 5 PYLL Mortality Causes in Canada, 2001

1. Neoplasm
2. Circulatory disease
3. Unintentional injuries
4. Suicide
5. Respiratory disease

Source: Statistics Canada. *Health Indicators*, 2001. Catalogue No.82-311-XE

Innovation-Diffusion Theory

- theory that describes the process by which health promotion efforts spread in populations
- aims to identify the most effective methods of health promotion within a population
- **Roger's diffusion theory** illustrates the following hierarchy within populations:
 - early adapters (community leaders)
 - early majority
 - late majority group
 - late adapters

Measurements of Health and Disease in a Population

Life Expectancy

- the average number of years that an individual will live
- usually qualified by country, gender, and age

Crude Death Rate

- mortality rate from all causes of death per 1,000 in the population

Age Standardized Rate

- adjustment made to the crude rate of a health-related event in a specific population when compared to a "standard" population
- standard population is one with a fixed number of persons in each age and sex group (e.g. the 1991 census data for Canada using 5 year age groups for males and females)
- adjustment can be made on the basis of any characteristics of a population
- standardization prevents bias which could be made by comparing crude rates from two dissimilar populations (e.g. crude death rates between decades are not comparable as the population age distribution has changed with time)

Standardized Mortality Rate

- the ratio of the observed (actual) number of deaths to the expected number of deaths for a group (e.g. age, race, gender, etc.)
- useful for comparing populations that are significantly different in some aspect (e.g. the causes of death in developing and developed countries)

Potential Years of Life Lost (PYLL)

- calculated for a population using the difference between the actual age of death and a standard age of death
- increased emphasis is therefore given to mortality at a younger age
- males are more likely to die at younger ages due to unintentional injuries; this causes PYLL to be higher in males than females

Infant Mortality Rate (IMR)

- number of deaths among children under 1 year of age reported during a given time period divided by the number of live births reported during the same time period and expressed per 1,000 live births

Maternal Mortality Rate (MMR)

- annual number of deaths of women during pregnancy and due to puerperal causes per 100,000 live births

Proportional Mortality Ratio (PMR)

- proportion of deaths in a specified population over a given period of time attributable to a specific cause
 - each cause is expressed as a percentage of all deaths, with the sum of all causes adding to 100%
- these proportions are not mortality rates, as the denominator is all deaths and not the specific population in which the deaths occurred

Disability Adjusted Life Year (DALY)

- quantitative indicator of the burden of disease that reflects the total amount of healthy life years lost
- includes loss from premature mortality or loss due to a degree of disability over a specific period of time; these disabilities can be physical or mental
- two purposes:
 1. measure the burden of disease
 2. increase the budget allocative efficiency by identifying health interventions that will afford the largest improvement in health

Quality Adjusted Life Year (QALY)

- a value from 0 to 1 assigned to a year of life based on its quality, a year in perfect health is considered equal to 1 QALY, the value of a year in ill health would be lowered based on the burden of disease

For additional rate calculations, see *Outbreak of Infectious Diseases*, PH20

Epidemiology

Definitions

Population

- a collection of individuals who share a common trait. Most commonly applied to a geographic area but it could be another factor such as ethnic group

Sample

- a selection of individuals from a population or set of possible observations
- types:
 - random – all are equally likely to be selected
 - systematic – an algorithm is used to randomly select a subset
 - stratified – separate representations of more than one subgroup
 - cluster – grouped in space/time to reduce costs
 - convenience – non-random

Sample Size

- sample size contributes to the statistical precision of the estimate
- increasing the sample size decreases the probability of type I and type II errors

Bias

- non-random error leading to a deviation of inferences or results from the truth
- any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth
 - lead-time:** time between early diagnosis with screening and when diagnosis would have been made without screening
 - lead-time bias:** over-estimation of survival when the estimate is made from the time of actual diagnosis, instead of the time when the disease would have been diagnosed without screening (see Figure 3)
 - incidence-prevalence bias:** when prevalent cases include long-term survivors who have a better prognosis than incident cases
 - length time bias:** overestimation of the survival time due to the sampling of prevalent as opposed to incident cases
 - selection of prevalent cases will favour the over-inclusion of longer-living cases rather than newly-diagnosed incident cases, some of whom may have short survival times
 - sampling bias:** occurs with the selection of a sample that does not truly represent the population
 - sampling procedures should be chosen to prevent or minimize bias
 - recall bias:** when individuals with a disease are more prone to recalling or believing they were exposed to a possible causal factor than those who are free of disease

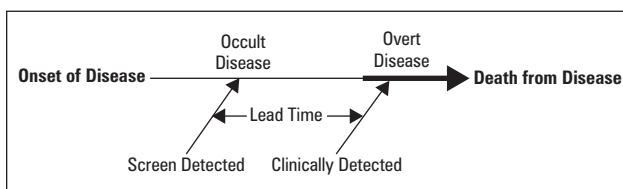


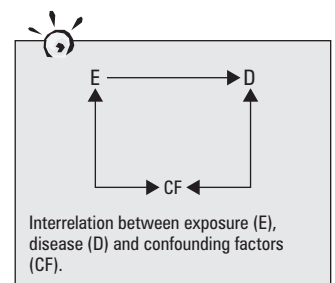
Figure 3. Lead Time Bias

Confounder

- a variable that is related to both the exposure and outcome but is not measured or is not distributed equally between groups
- distorts the apparent effect of an exposure or risk because it is not logically possible to separate the contribution of a single causal factor to an effect (e.g. smoking and alcohol with head and neck cancer)

Prevalence

- total number of cases in a population over a defined period of time (see sidebar)
- two forms of prevalence
 - point prevalence:** attempts to measure the frequency of all disease at one specific point in time, therefore knowledge of the time of onset of disease is not required
 - period prevalence:** measure constructed from prevalence at a point in time, plus new cases and recurrences over a defined period of time
- depends on **incidence rate** (see sidebar) and disease duration from onset to termination
- favours the inclusion of chronic over acute cases and therefore presents a biased picture of the disease
- prevalence studies are cross-sectional and cannot be used for causal inferences
- prevalence figures are useful for determining the extent of a disease and can aid in the rational planning of facilities and services



Incidence and Prevalence

Incidence = $\frac{\text{number of new cases of disease in a time interval}}{\text{total population at risk} \times [\text{per unit population (e.g. 100,000)}]}$
(measures the rate of new infections)

Prevalence = $\frac{\text{number of existing cases of disease at a point in time}}{\text{total population} \times [\text{per unit population (e.g. 100,000)}]}$
(measures the frequency of disease at a point in time)

Figure 4. Understanding Sensitivity and Specificity

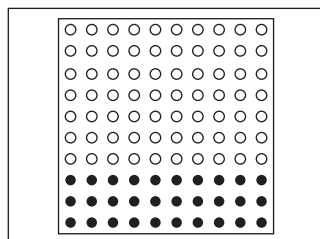


Figure 4a. Hypothetical Population

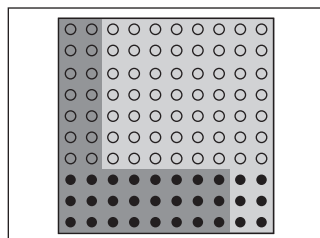


Figure 4b. Results of Diagnostic Test on Hypothetical Population

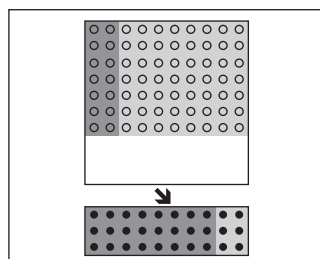


Figure 4c. Sensitivity of Test
(e.g. $24/30 = 80\%$ sensitive)

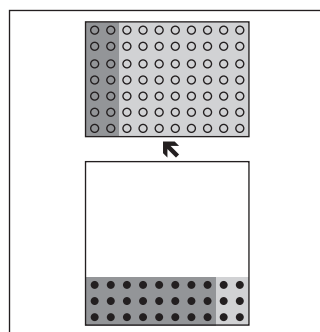


Figure 4d. Specificity of Test
(e.g. $56/70 = 80\%$ specific)

○ – well person
● – person with disease
Dark grey – positive test result
Light grey – negative test result

Source: Loong TW. Understanding sensitivity and specificity with the right side of the brain. *BMJ* 2003; 327:716-719

Sensitivity

- proportion of people with disease who are correctly identified by a positive test

Specificity

- proportion of people without disease who are correctly identified by having a negative test

Likelihood Ratio (LR)

- likelihood that a given test result would be expected in a patient with disease compared with the likelihood that the same result would be expected in a patient without disease
- LR+ indicates how much the probability of disease increases if the test is positive
- LR- indicates how much the probability of disease decreases if the test is negative

Positive Predictive Value (PPV)

- proportion of people with a positive test who have the disease

Negative Predictive Value (NPV)

- proportion of people with a negative test who are free of disease

Pre-test Probability

- an estimate of the likelihood a particular patient has a given disease based on known factors

Post-test Probability

- a revision of the probability of disease after a patient has been interviewed and examined
- calculation process can be more explicit using results from epidemiologic studies, knowledge of the accuracy of tests and Bayes' theorem
- the post-test probability from clinical examination is the basis of consideration when ordering diagnostic tests or imaging studies
 - after each iteration the resultant post-test probability becomes the pre-test probability when considering new investigations

Intention-To-Treat

- a strategy for analyzing data in which all participants are included in the group to which they were assigned, whether or not they completed the requirements of that group
- this is to limit the bias introduced by issues of compliance and to simulate real world situations in which not all patients comply

Relative Risk (RR)

- ratio of the incidence of a health outcome among the exposed population to the incidence of the health outcome in the non-exposed population

Attributable Risk (AR)

- rate of a health outcome attributable to a hypothetical risk factor for that outcome
- incidence in exposed population] - [incidence in non-exposed]
- attributable risk assumes causation

Odds Ratio (OR)

- ratio of the odds of exposure to a hypothetical risk factor among cases to the odds of exposure among non-cases
- can be interpreted as the ratio of the odds of developing the outcome (e.g. disease) among those exposed to the hypothetical risk factor to those who are not exposed
- OR approximates RR when the prevalence of disease in the population is low

Source: Last JM. *A Dictionary of Epidemiology*, 4th ed. Oxford University Press. 2001.

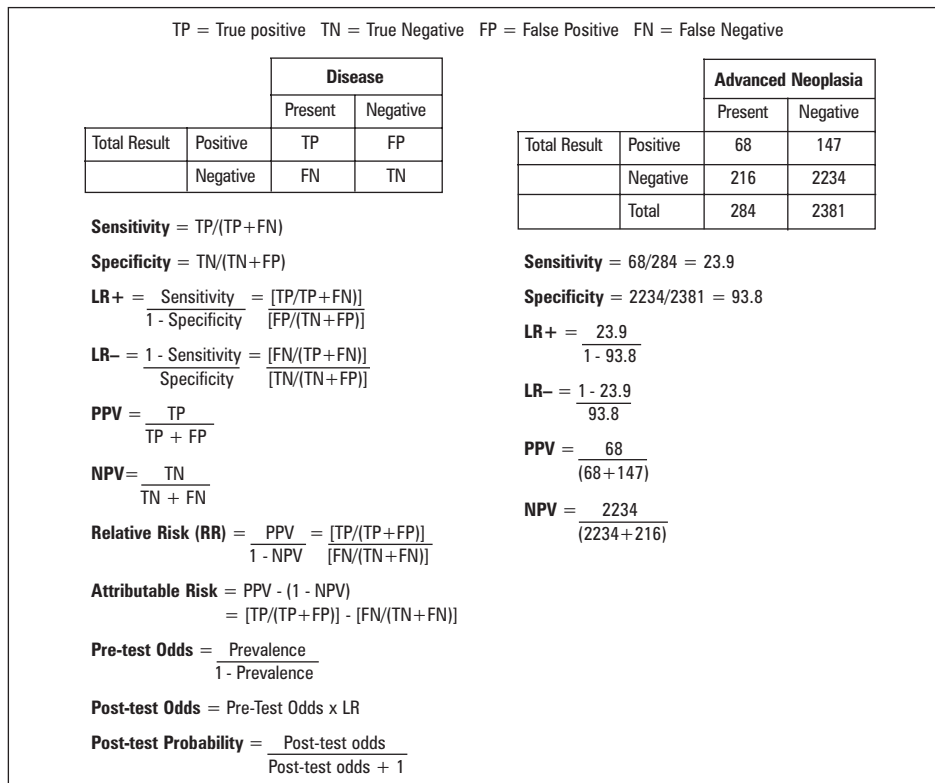


Figure 5. Clinical Epidemiology Equations with Examples from FOBT Testing for Advanced Neoplasia
 Numbers from Collins J, Lieberman D, Durbin T, Weiss D. Accuracy of Screening for Fecal Occult Blood on a Single Stool Sample Obtained by Digital Rectal Examination: A Comparison with Recommended Sampling Practice. *Annals of Internal Medicine* 2005; 142 (2): 81-85

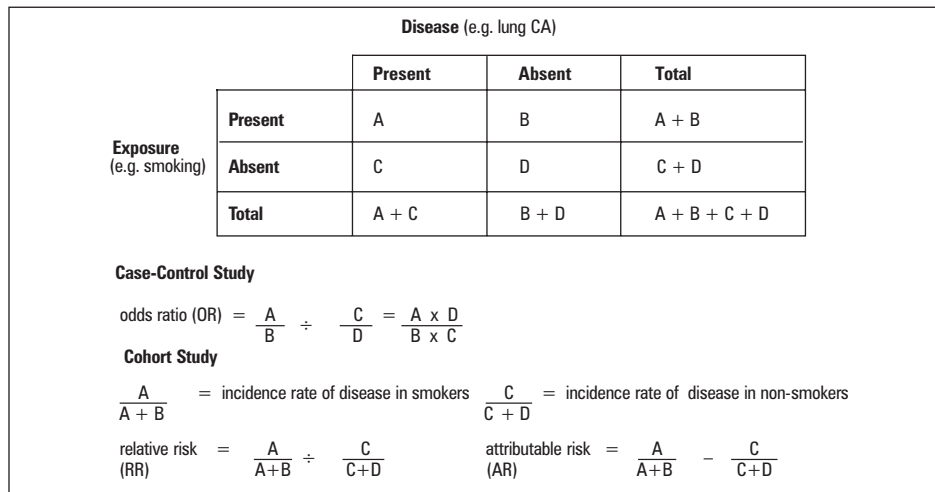
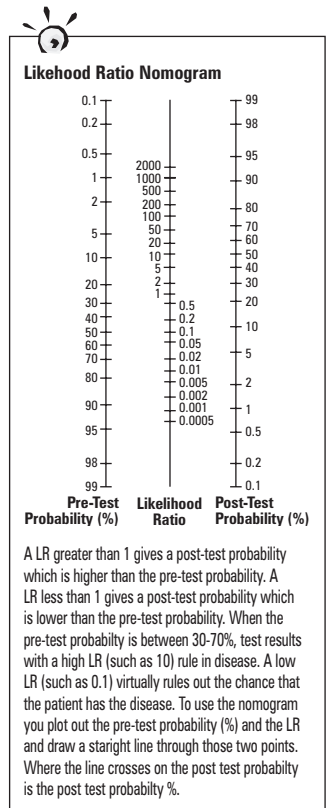
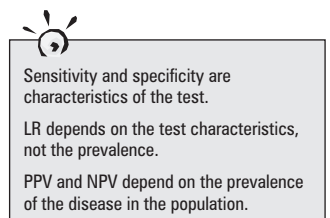
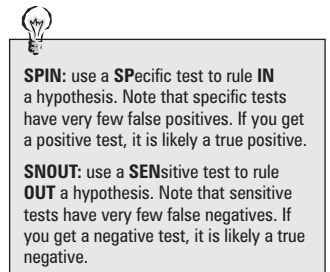


Figure 6. Results Tabulation by Study Design



**Formulating A Research Question****PICO**

Patient Characteristics

Intervention of Interest

Comparison Group or Control Group

Outcome that you are trying to prevent or achieve



An example of an ecological study would be one looking at the association between smoking rates and lung cancer rates in different countries.



An example of a cross sectional study is one that examines the distribution of BMI by age in Ontario at a particular point in time.

Types of Study Design

Observational Studies

- ecological study
- prevalence study (cross-sectional)
- case-control study (retrospective)
- cohort study (prospective, incidence, longitudinal)

Experimental Studies

- non-randomized control trials (e.g. allocation by clinic or other non-random basis) can be performed when randomization is not possible
- randomized controlled trial (RCT)
- **clinical trial**: tests a treatment or laboratory test in human subjects

Ecological Study

Definition

- observational study of an aggregate

Subjects

- population rather than individuals (e.g. geographic areas such as countries or census tracts)

Methods

- hypotheses generated, often providing accurate descriptions of the average exposure or risk of disease for a population

Advantages

- quick, easy to do, makes use of readily available data

Disadvantages

- cannot be used for direct assessment of causal relationships because adequate control of all confounding variables cannot be achieved
- cannot infer about an individual in the population; this is an ecological fallacy
 - e.g. an ecological study may show that France has a higher rate of red wine consumption and a lower rate of death from cardiovascular (CVS) causes
 - in the above case, one cannot conclude that red wine drinking leads to lower risk of death from CVS disease because the individuals dying from CVS disease were not investigated for their red wine drinking habits

Prevalence Study (Cross-Sectional)

Definition

- status of individuals with respect to presence and absence of both exposure and disease, assessed at one point in time

Subjects

- a population (total or sample)

Methods

- collect information from each person at one particular time (or retrospectively from one particular time)
- tabulate the numbers in groups (e.g. by presence or absence of disease and presence or absence of a factor)
- do appropriate analysis (e.g. make 2 x 2 table and compare groups)

Advantages

- allows for determination of association between variables

Disadvantages

- does not allow for assessment of temporal relationship between variables

Case-Control Study (Retrospective)

Definition

- samples a group of people who already have a particular outcome (cases) and compares them to a similar sample group without that outcome (controls)

Subjects

- two study populations are compared: cases and controls

Methods

- retrospective
- ask cases and controls about exposures; hypothesizes that cases have had significantly more exposure to the risk factors than controls
- select all the cases of a specific disease during a specific time frame
 - cases should be representative of spectrum of clinical disease under investigation
- select control(s)
 - controls should represent the general population
- to minimize risk of bias, may select more than one control group and/or match controls to cases (e.g. age, gender)
- if a presumed risk factor is present in cases significantly more frequently than in controls, then an association exists between the risk factor and the disease (expressed as an **odds ratio**, an estimate of relative risk)



An example of a famous case control study is by Sir Richard Doll who demonstrated the link between tobacco smoking exposure and lung cancer cases.

Advantages

- commonly used when disease in population is rare (less than 10% of population) due to increased efficiency
- less costly and time consuming than cohort studies

Disadvantages

- may suffer from recall bias (see PH9 for definition)
- confounding may occur
- selection bias for controls
- only one outcome can be measured

Cohort Study (Prospective, Incidence, Longitudinal)

Definition

- subjects are sampled and, as a group, classified on the basis of presence or absence of exposure to a particular risk factor

Subjects

- population separated into cohorts
 - cohort is a group of people with a common characteristic (e.g. year of birth, place of residence, occupation, exposure to a suspected cause of disease)
 - cohort is divided into exposed vs. non-exposed groups due to inherent characteristics of participants (e.g. smoking, diet, exercise, etc.)

Methods

- subjects are followed for a specific period of time (often years) to determine development of disease in each exposure group
- start with persons who are free of disease and follow forward for a period of time
- measure exposure to a risk factor (e.g. smoking)
- define one or more outcomes
- collect information on factors from all persons at the beginning of the study
- tabulate the number of persons who develop the disease or other measured outcomes of morbidity
- provides estimates of incidence, relative risk, attributable risk

Advantages

- can show an association between a factor and an outcome/several outcomes
- generally provides stronger evidence for causation than case-control study

Disadvantages

- by itself, cannot establish causation
- confounding factors are common as the cohort self-selects the exposure
- cost and duration of time needed to follow cohort are high

Randomized Controlled Trial (RCT)

Definition

- subjects are randomly assigned to two or more groups, one of which is the control group, the other group(s) receive(s) an experimental intervention

Subjects

- individuals are separated into groups of exposures; these exposures are assigned by a random process rather than by known reasons

Methods

- random distribution of individuals into two or more treatment groups
- one group receives placebo or standard therapy
- one or more groups receive(s) the intervention(s) under study
- the outcome is measured and the groups are compared
- all other conditions are kept the same between groups

Advantages

- “gold standard” of studies, upon which the practice of EBM is founded
- provides the strongest evidence for causation
- with sufficient sample size and appropriate randomization, confounding variables are minimized
- allows prospective assessment of the effects of intervention without introducing bias

Disadvantages

- some concepts are not amenable to randomization (e.g. cannot randomize subjects to poverty/wealth or to harmful exposures such as smoking)
- costly

Considerations**A. What is the method of randomization?**

- is it a centralized concealed process?
- **single-blind:** subjects do not know group assignment (intervention or placebo)
- **double-blind:** subject and observer both unaware of group assignment
- **triple-blind:** subject, observer, and analyst unaware of group assignment (rarely done)

B. Are the groups truly randomized?

- are the groups balanced on demographics and other potential confounders?
- if not, was there selection bias in group assignment?

C. Is the follow-up of sufficient duration to assess potential harm? How many subjects have been lost to follow-up?**D. Are the groups treated equally except for the intervention being studied?****E. Are the outcomes meaningful?**

Meta-Analysis

Definition

- combines the results of independent studies that address a common research hypothesis into one large study

Subjects

- combination of all the subjects used in original studies

Methods

- selection of studies from the published literature
- statistical models used to combine the results of each independent study

Advantages

- attempts to overcome the problem of reduced power due to small sample sizes
- ability to control for inter-study variation

Disadvantages

- sources of bias may not be controlled for
- reliance on published studies may increase the effect as it can be difficult to publish studies that show no significant results (publication bias)
- the decision to include/reject a particular study is subjective

Qualitative Studies

Definition

- a study undertaken to understand complex social phenomena

Method

- inductive approach primarily concerned with discovery and description
- in depth interviewing, participant observation, and focus groups are the major data collection techniques
- hypotheses often developed during the research
- analysis can be in narrative rather than numerical form

Advantages

- can be used for exploratory or hypothesis generating purposes
- open ended questions and flexible study design
- provides descriptions of how people experience a research issue

Disadvantages

- labour intensive
- difficult to replicate findings
- researcher bias

Critical Appraisal



Assessing Evidence

- critical appraisal is the process of systematically examining research evidence to assess validity, results, and relevance before using it to inform a decision

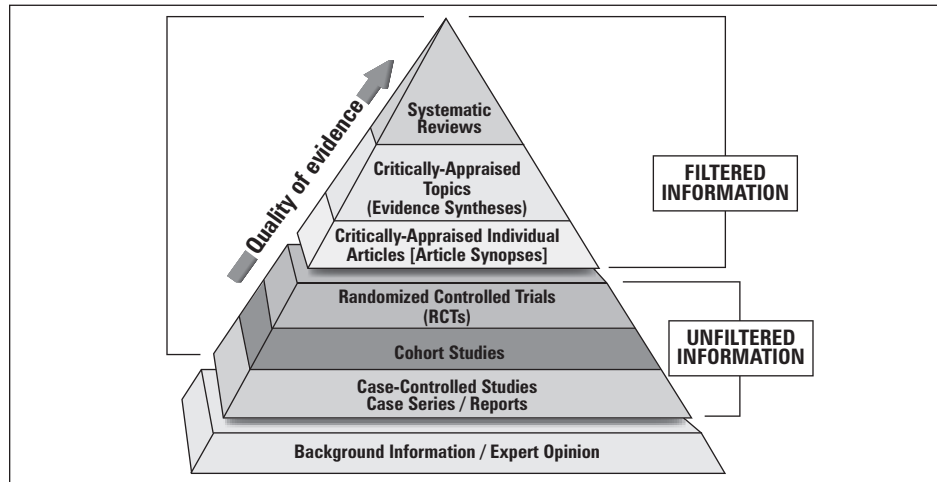


Figure 7. Pyramid of Pre-Appraised Evidence

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A. Are the results of the study valid?

- see below for classifications of evidence that has already been assessed; see sidebar for assessing primary studies

B. What are the results?

- what was the impact of the treatment effect?
- how precise was the estimate of treatment effect?
- what were the confidence intervals and power of the study?

C. Will the results help me in caring for my patients?

- are the results clinically significant?
- can I apply the results to my patient population?
- were all clinically important outcomes considered?
- are the likely treatment benefits worth the potential harm and costs?

Levels of Evidence: Classifications Cited in Guidelines/Consensus Statements

Level I evidence: based on RCTs (or meta-analysis of RCTs) big enough to have low risk of incorporating FP or FN results

Level II evidence: based on RCTs too small to provide Level I evidence; may show positive trends that are non-significant, or have a high risk of FN results

Level III evidence: based on non-randomized, controlled or cohort studies; case series; case-controlled; or cross-sectional studies

Level IV evidence: based on opinion of respected authorities or expert committees, as published consensus conferences/guidelines

Level V evidence: opinions of the individuals who have written/reviewed the guidelines (i.e. Level IV evidence), based on experience/knowledge of literature/peer discussion

Notes: These 5 levels of evidence are not direct evaluations of evidence quality or credibility; they reflect the nature of the evidence. While RCTs tend to be most credible (with <III), level III evidence gains credibility when multiple studies from different locations and/or time periods report consistent findings. Level IV and V evidence reflects decision-making that is necessary but in the absence of published evidence.

Figure 8. Levels of Evidence Classifications

Note: this is only one method of classifying evidence. Various systems exist, but operate within the same premise that certain types of evidence carry more weight than others.

Data Analysis

Statistical Hypotheses

- null (H_0)**
 - no relationship exists between the two stated variables, i.e. no association between the proposed risk factor and the disease
- alternative (H_1)**
 - a relationship does exist between the two stated variables



Validity

- The degree to which the outcome observed in the study can be attributed to the intervention

5 Questions About the Validity of Primary Studies

1. Were the patients randomized?
2. Was the follow-up of patients sufficiently long and complete?
3. Were all patients analyzed in the groups to which they were randomized?
4. Were the groups treated equally except for the intervention?
5. Were the patients and clinicians kept blind to treatment?

Other Questions to Consider

- Were the groups similar (i.e. demographics, prognostic factors) at the start of the trial?
- Were the appropriate and valid exposure and outcome measures obtained?
- Were outcome assessors aware of group allocation?
- Was contamination reported?
- Were ethical issues continuously upheld?



Canadian Task Force on Preventive Health Care Grading of Health Promotion Actions

A: Good evidence to recommend the preventive health measure

B: Fair evidence to recommend the preventive health measure

C: Existing evidence is conflicting and does not allow making a recommendation for or against use of the clinical preventive action, however other factors may influence decision-making

D: Fair evidence to recommend against the preventive health measure

E: Good evidence to recommend against the preventive health measure

I: Insufficient evidence (in quantity and/or quality) to make a recommendation, however other factors may influence decision-making

Source: Canadian Task Force on Preventive New Grades for Recommendations from the Canadian Task Force on Representative Healthcare. CMAJ 2003; 169(3): 207-208.

Type I Error (α Error)

- the null hypothesis is falsely rejected (e.g. stating intervention X is effective when it is not, or declaring an observed difference to be real rather than by chance)
- the probability of this error is denoted by the p-value
- studies tend to minimize this type of error, since a type I error can have larger clinical significance than a type II error

Type II Error (β Error)

- the null hypothesis is falsely accepted (e.g. stating intervention X is not effective when it is, or declaring an observed difference/effect to have occurred by chance when it is present)
- higher level of error is acceptable for most studies
- can also be used to calculate statistical power

Power

- probability of correctly rejecting a null hypothesis when it is in fact false, i.e. the probability of finding a specified difference to be statistically significant at a given p-value
- power increases with an increase in sample size
- power = $1 - \beta$, and is therefore equal to the probability of a true positive result

Statistical Significance

- the probability that the statistical association found between the variables is due to random chance alone (i.e. that there is no association)
- the preset probability is set sufficiently low that one would act on the result; frequently $p=0.05$
- when statistical tests result in a probability less than the preset limit, the results are said to be statistically significant, i.e. $p<0.05$

Clinical Significance

- measure of clinical usefulness (e.g. 1 mmHg BP reduction may be statistically significant, but may not be clinically significant)
- depends on factors such as cost, availability, patient compliance, and side effects in addition to statistical significance

Trend

- an observed directional relationship that does not meet criteria for statistical significance and thus should be interpreted with caution

Confidence Interval (CI)

- provides a range of values within which the true population mean lies
- frequently reported as 95% CI (e.g. one can be 95% certain that the true value is within this data range)
- bounded by the upper and lower confidence limits

Data

- information collected about a sample or population
- there are 3 classes of data listed with examples:
 - discrete** – e.g. number of strokes experienced
 - continuous** – e.g. serum cholesterol, hemoglobin, age
 - categorical** – e.g. gender, marital status

Accuracy

- how closely a measurement approaches the true value

Reliability

- how consistent a measurement is when performed by different observers under the same conditions or by the same observer under different conditions

Validity

- extent to which a measurement approaches what it is designed to measure
- determined by the accuracy and reliability of a test

Internal Validity

- degree to which the findings of the sample truly represent the findings in the study population
- dependent on the precision and accuracy

External Validity

- degree to which the results of the study can be generalized to other situations or populations



A confidence interval which includes 1 implies the results are not statistically significant

A wider confidence interval implies more variance than a tighter confidence interval.

**Accuracy versus Reliability**

Good reliability
Good accuracy



Poor reliability
Good accuracy



Good reliability
Poor accuracy



Poor reliability
Poor accuracy

Effectiveness of Interventions

DEFINITIONS

Relative Risk Reduction (RRR)

- proportional reduction in rates of bad outcomes between experimental and control participants in a trial

Absolute Risk Reduction (ARR)

- absolute arithmetic difference in rates of bad outcomes between experimental and control participants in a trial
- events occur more often in control group than in experimental group

Absolute Risk Increase (ARI)

- absolute arithmetic difference in rates of bad outcomes between control and experimental participants in a trial
- events occur more often in experimental group than in control group

Number Needed to Treat (NNT)

- number of patients who need to be treated to achieve one additional favourable outcome, calculated as $1/(\text{ARR})$
- only one of many factors that should be taken into account in clinical decision making (e.g. must take into account cost, ease, feasibility, etc. of intervention)
 - a condition with death as a potential outcome can have a higher NNT (and be acceptable), as compared to an intervention to prevent an outcome with low morbidity, in which a low NNT would be necessary

Number Needed to Harm (NNH)

- number of patients who, if they received the experimental treatment, would lead to one additional patient being harmed, compared with patients who received the control treatment, calculated as $1/(\text{ARI})$

Adherence (formerly compliance)

- degree to which a patient adheres to a treatment plan

Effectiveness, Efficacy, Efficiency

- three measurements indicating the relative value (beneficial effects vs. harmful effects) of an intervention
- efficacy:** the extent to which a specific intervention produces a beneficial result under ideal conditions
 - ideally, based on the results of a randomized control trial (the theoretical impact)
- effectiveness:** measures the benefit of an intervention under usual conditions of clinical care
 - considers both the efficacy of an intervention and its actual impact on the real world, taking into account access to the intervention, whether it is offered to those who can benefit from it, its proper administration, acceptance of intervention, and degree of adherence to intervention
- efficiency:** a measure of economy of an intervention with known effectiveness
 - considers the optimal use of resources (e.g. monetary, time, personnel, equipment, etc.)



Equations to Assess Effectiveness

$\text{CER} = \text{control group event rate}$
 $\text{EER} = \text{experimental group event rate}$
 $\text{RRR} = (\text{CER} - \text{EER})/\text{CER}$
 $\text{ARR} = \text{CER} - \text{EER}$
 $\text{ARI} = \text{EER} - \text{CER}$
 $\text{NNT} = 1/\text{ARR}$
 $\text{NNH} = 1/\text{ARI}$



Beware:

Do not be swayed by a large RRR, as it may appear to be large if event rate is small to begin with. In these cases ARR is more accurate (e.g. a drug which lowers an event which occurs in 0.1% of a population to 0.05% can boast a RRR of 50%, and yet the ARR is only 0.05%, which is not nearly as impressive).

Common Statistical Tests

Z-Test (known as t-test for samples of fewer than 30 points)

- designed to test the difference between two sample means for continuous data

Chi-square Test (χ^2)

- designed to test the correspondence between a theoretical frequency distribution and an observed frequency distribution of categorical data
 - if one sample of 20 patients is 30% hypertensive and another comparison group of 25 patients is 60% hypertensive, a chi-squared test can be used to determine if this variation is different than might be expected due to chance alone

Analysis of Variance (ANOVA)

- similar to the Z/t-test, but compares mean values from three or more groups simultaneously considering one or more factors
- one-way ANOVA compares 2 or more groups considering one factor
- two-way ANOVA compares 2 or more groups considering two or more factors
 - the blood pressure reductions in groups that have undergone some combination of two possible interventions: an education program and on-site therapy

Regression

- **linear regression**
 - a technique used to describe the relationship between two continuous variables, where one variable might be used to predict or to explain changes in the other, though not necessarily causal
 - assumes a linear relationship between variables
 - the slope of the line of best fit can be estimated
- **logistic regression**
 - requires discrete outcomes (e.g. disease or disease-free)
 - may produce an adjusted odds ratio for individual variables

Distributions

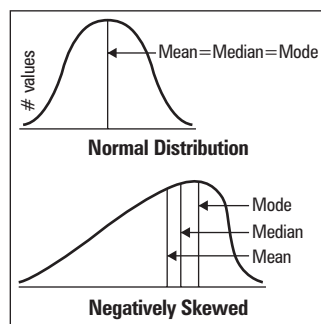


Figure 9. Distribution Curves

- distribution describes the probability of events
- normal (Gaussian) or non-normal (skewed, bimodal, etc.) (see Figure 9)
- characteristics of the normal distribution
 - mean = median = mode
 - 67% of observations fall within one standard deviation of the mean
 - 95% of observations fall within two standard deviations of the mean
- measures of central tendency
 - **mean**: sum of all observations divided by total number of variables
 - **median**: value at the 50th percentile, this is a better reflection of the central tendency for a skewed distribution
 - **mode**: most frequently observed value in a series
- measures of dispersion
 - **range**: the largest value minus the smallest value
 - **variance**: a measure of the spread of data
 - ♦ average squared deviation of each number from the mean of a data set
 - **standard deviation**: the average distance of data points from the mean (the positive square root of variance)
- given the mean and standard deviation of a normal or binomial distribution curve, a description of the entire distribution of data is obtained

Causation

Criteria for Causation (Sir Bradford Hill)

1. **strength of association**: the frequency with which the factor is found in the disease and the frequency with which it occurs in the absence of disease
2. **consistency**: is it the same outcome with different populations or study design?
3. **specificity**: is the association particular to your intervention and measured outcome?
4. **temporal relationship**: did the exposure occur before the onset of the disease?
5. **biological gradient**: finding a quantitative relationship between the factor and the frequency (e.g. dose response relationship)
6. **biological plausibility**: does the association/causation make biological sense?
7. **coherence**: can the relationship be explained/accounted for based on what we know about the laws of science, logic, etc.?
8. **experimental evidence**: experiment that investigates what happens when the suspected offending agent is removed (e.g. is there improvement?)
9. **analogy**: do other established associations provide a model for this type of the relationship?

Note: not all criteria must be fulfilled to establish scientific causation, and the modern practice of EBM emphasizes 'experimental evidence' as superior to other criteria



Beware:

Correlation ≠ Causation

e.g. There is a direct correlation between the amount of ice cream sold and the amount of deaths in swimming pools. Of course, ice cream does not cause drowning, rather, they both increase in the summer.



Continuous Quality Improvement (CQI)

- Edward Deming's Philosophy on Quality:
 - quality = $\frac{\text{result of work effort}}{\text{cost}}$
- according to Deming's philosophy, as quality increases, cost decreases – there is an inverse relationship
- CQI used to analyze *systems*
 - **systems**: collection of processes that is organized around a purpose

Systems Analyses Tools

1. **5 Whys:** brainstorming tool to get to root of a problem, which simplifies the process of change – continue to ask 'why' until the root of the problem is discovered
2. **Ishikawa Diagrams (aka Fishbone Diagrams):** identify generic categories of problems that have an overall contribution on the effect (see Figure 10)

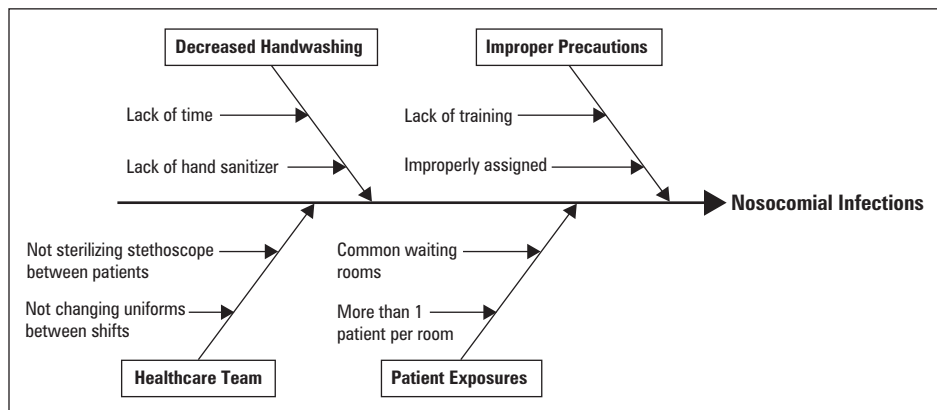


Figure 10. Ishikawa Diagram

3. **Defect check sheets:** consider all defects and tally up the number of times the defect occurs
4. **Pareto Chart:** y vs. x chart; x axis = defect categories, y-axis = frequency; plot cumulative frequency on the right y-axis (see Figure 11)
 - purpose is to highlight most important among large set of factors

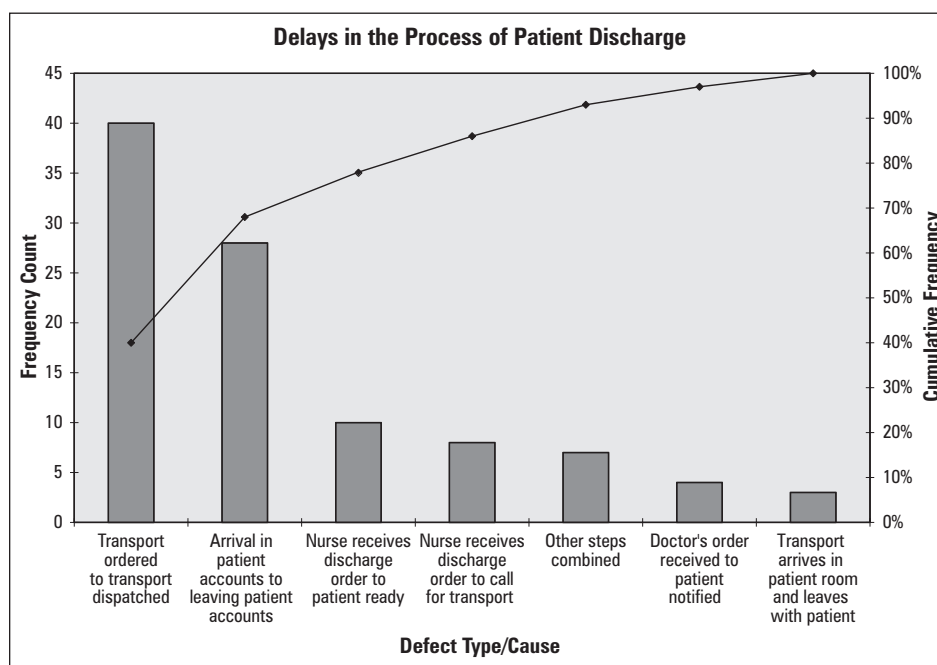


Figure 11. Pareto Chart: Factors Affecting Delay in Patient Lab Results

Cost Analysis

Cost Benefit Analysis

- a process of, either explicitly or implicitly, weighing the total expected costs against the total expected benefits of one or more actions in order to choose the best or most profitable option
- all costs are adjusted for the time value of money, so that costs that may change over time are expressed on a common basis in terms of their present value

Cost Effectiveness Analysis (CEA)

- a comparison of the relative expenditure (costs) and outcomes (effects) of two or more courses of action
- cost-effectiveness analysis is often used where a full cost benefit analysis is inappropriate
- a CEA is commonly expressed in terms of a ratio: the denominator is a gain in health from a measure (e.g. years of life, premature births averted, sight-years gained) and the numerator is the cost of the health gain
- the most commonly used outcome measure is quality-adjusted life years (QALY)

Outbreak of Infectious Diseases

Definitions

Outbreak

- occurrence of new cases clearly in excess of the baseline frequency of the disease in a defined community or population over a given period of time
- synonymous with epidemic, although generally considered to be an epidemic that is localized, has an acute onset, or is relatively short in duration

Epidemic

- any disease, infectious or chronic, occurring at a greater frequency than usually expected in a defined community or institutional population over a given time period (e.g. excessive rate of disease)

Endemic

- constant presence of disease or infectious agent in a given geographic area or population subgroup (e.g. usual rate of disease)

Pandemic

- epidemic over a wide area, crossing international boundaries, and affecting a large number of people

Attack Rate

- cumulative incidence of infection within a defined group observed during a specific period of time in an epidemic
- calculated by dividing the total number of people who develop clinical disease by the population at risk, usually expressed as a percentage

Secondary Attack Rate

- number of cases among contacts occurring within the incubation period following exposure to the primary case, in relation to the total exposed contacts
- infectiousness reflects the ease of disease transmission and is usually measured by the secondary attack rate

Pathogenicity Rate

- power of an organism to produce clinical disease in those that are affected

Virulence

- severity of the disease produced by the organism in a given host
- expressed as the ratio of the number of cases of severe and fatal infection to the total number of clinically affected

Case-Fatality Rate

- proportion of individuals contracting a disease who die as a result of that disease
- most frequently applied to a specific outbreak of acute disease in which all patients have been followed for an adequate period of time to include all attributable deaths
- must be clearly differentiated from the mortality rate

Mortality Rate/Death Rate

- estimation of the portion of the population that dies during a specified period from all causes of death

All-Cause Mortality Rate

- estimation of the portion of the population in a given age group that dies during a specific period from all causes of death for that age group

Morbidity Rate

- estimation of the portion of the population that suffers illness or ill health during a specified period

**Infection Control Precautions****Contact** (impetigo, chicken pox, warts)

- Wash hands
- Gloves
- Gown
- Wipe equipment after use

Airborne (TB)

- Contact precautions PLUS
- N95 mask (fit tested)
- Negative Pressure Room

Droplet (influenza, mumps, pneumonia)

- Contact precautions PLUS
- Goggles/face shield
- Surgical mask

Steps to Control an Outbreak

1. Define the Problem

- is it an outbreak? (PH20)

2. Appraise Existing Data and Institution of a Surveillance System

- **case definition:** formulated from the most common symptoms or signs; definition includes the likely date of onset of illness of the first case (e.g. any person with onset of fever higher than 38.5°C and cough within past 28 days)
 - laboratory confirmation of the clinical diagnosis via culture or serology is sought as soon as possible as results can define a case more precisely
- **active surveillance:** identify those who may have been exposed to the infectious agent and who fit the case definition through active efforts, including:
 - contacting emergency rooms, physicians' offices, local schools
 - obtaining records from other health units, mortality, or laboratory records

3. Formulate Hypotheses and Implementation of Initial Control Measures

- depends on symptoms, suspected agent, population at risk, and location
- effective outbreak management includes infection control when outbreak is due to infectious agent

4. Test the Hypothesis through Analysis of Surveillance Data or Special Studies

- analyze raw data and generate epidemic curves

5. Draw Conclusions, Re-Adjust Hypothesis, and Control Measures

6. Write Report, Make Recommendations for Long-term Prevention, and Surveillance

- modify control measures to stop the outbreak
 - remove/neutralize agent (e.g. isolating residents in a facility)
 - strengthen resistance of hosts (e.g. immunization)
 - interrupt means of transmission in environment (e.g. improvements in food processing)
- communicate outbreak information to the public in an effective manner
 - provide education
 - recommend specific prevention and control strategies clearly
 - deliver a unified message (e.g. local public health department, Chief Public Health Officer)

For specific examples, see "Communicable Diseases" section in: Shah CP. *Public Health and Preventive Medicine in Canada*. 5th edition. Elsevier Canada. 2003.



Steps to Controlling an Outbreak

- Surveillance
- Defining purpose
- Data collection
- Data analysis
- Interpretation
- Dissemination
- Action to prevent disease/injury

Active Surveillance

Outreach such as visits or phone calls by the public health/surveillance authority to detect unreported cases (e.g. an infection control nurse goes to the ward and reviews temperature charts to see if any patient has a nosocomial infection)

Passive Surveillance

A surveillance system where the public health/surveillance authority depends on others to submit standardized forms or other means of reporting cases (e.g. ward staff notify infection control when new cases of nosocomial infections are discovered)

Epidemic Curves

Epidemic Curve

- generated from surveillance data
- usually a frequency histogram, with the number of cases plotted on the vertical axis and their dates or times of onset along the horizontal axis
- curve can indicate whether the epidemic (outbreak) has a common source or whether it is propagated

Common-Source Epidemics

- people become ill because of exposure to a single (common) source of infection
- **point source epidemic:** exposure is brief and essentially simultaneous (see Figure 12a)
- **extended source epidemic:** exposure lasts for a period of days to weeks
 - extended exposure can be continuous (no irregular peaks, see Figure 12b) or intermittent (irregularly spaced peaks)

Propagated Epidemic

- begins with only a few exposed persons but is maintained by person-to-person transmission (e.g. measles/influenza); epidemic curve shows a series of peaks (see Figure 12c)

Figure 12. Epidemic Curves

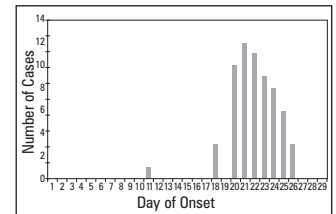


Figure 12a. Point Source Epidemic Curve

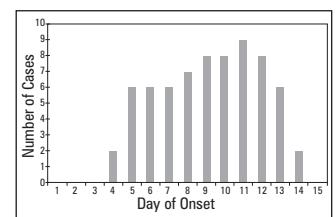


Figure 12b. Common Continuous Source Epidemic Curve

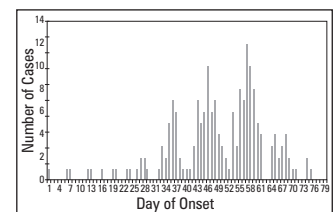


Figure 12c. Propagated Source Epidemic Curve

Environmental Health

Definition

- study of conditions in the natural and human-made environment that influence human health and well-being
- environmental exposures
 - four main reservoirs: air, food, water, and soil
 - three main routes: inhalation, ingestion, or absorption (skin)
- usually divided into two main settings:
 - workplace: often high level exposure in healthy adults (see *Occupational Health*, PH25)
 - non-workplace: generally low level but chronic exposure; population at risk includes extremes of age, developing fetuses, and ill or immunocompromised individuals

Environmental Health Jurisdiction

Public Health Unit

- enforcement of water and food safety regulations (including restaurant food safety)
- sanitation
- assessment of local environmental risks
- monitoring and follow-up of reportable diseases

Municipal Government

- garbage disposal
- recycling

Provincial and Territorial Government

- water and air quality standards
- industrial emission regulation
- toxic waste disposal

Federal Government

- designating and regulating toxic substances
- regulating food products (e.g. Health Canada)
- setting policy for pollutants that can travel across provincial boundaries

International

- multilateral agreements (e.g. Kyoto Protocol, UN Convention on Climate Change, International Joint Commission)

Hazard Identification

- two major approaches
 - toxicological: examines the adverse effects of poisons on animals (including humans), has the potential to identify health hazards before humans become ill
 - epidemiological: provides information about health hazards in humans after humans have become ill

Air

Physical Contaminants

- sound waves
- ionizing radiation
 - radon is naturally produced by soil containing uranium or radium, can contaminate indoor air and is associated with a small proportion of lung cancers
 - ultraviolet radiation is increasing due to ozone layer destruction caused by chlorofluorocarbons (CFCs), and increases risk of skin cancer
 - alpha-particles are larger and damage the skin and bronchial lining (airway irritation)
 - beta-particles are smaller and cause deeper damage (alveoli)
- non-ionizing radiation
 - visible light, infrared, microwave

Chemical Contaminants

- ground-level ozone
 - main component of smog
 - worsens asthma, irritates upper airway
 - levels increasing in major cities

- carbon monoxide (fossil fuel related)
 - combustion byproduct
 - invisible, odourless gas
 - aggravates cardiac disease at low levels
 - headache, nausea, dizziness at moderate level
 - fatal at elevated concentrations
- sulphur dioxide (fossil fuel related), nitrogen oxides
 - contribute to acid rain
 - exacerbate breathing difficulties
- organic compounds (e.g. benzene, methylene chloride, tetrachloroethylene)
 - variety of health effects at high levels (e.g. benzene is a known carcinogen)
 - tend to be fat-soluble, easily absorbed through skin and difficult to excrete
- heavy metals (e.g. nickel, cadmium, chromium)
 - present in industrial emissions
 - variety of health effects: upper airway disease, asthma, decreased lung function
- second hand tobacco smoke
 - respiratory problems, increase risk of lung cancer

Biological Contaminants

- particulates (e.g. pollen, fungal spores, aerosols)
 - associated with decreased lung function, asthma, upper airway irritation
- biological agents
 - moulds thrive in moist areas; 10-15% of the population allergic
 - bacteria survive as spores and aerosols, can be distributed through ventilation systems (e.g. *Legionella*)
 - dust mites and pollens can trigger upper and lower-airway symptoms
 - ◆ dust mites are year-round and concentrate indoors
 - ◆ pollen is seasonal and outdoors

Climate Change

- anthropogenic greenhouse gas emissions (e.g. carbon dioxide, methane, etc.) leading to adverse changes in the global environment
 - increased extreme weather conditions (e.g. floods, hurricanes, heat waves)
 - increased distribution of vectors of disease (e.g. mosquitoes and malaria)
 - increased malnutrition from crop failures
 - increased diarrheal diseases

Water

Biological Contaminants

- mostly due to human and animal waste
- Aboriginal Canadians, rural Canadians at higher risk
- bacteria: *Escherichia coli* (e.g. Walkerton, ON), *Salmonella*, *Pseudomonas*, *Shigella*
- protozoa: *Giardia*, *Cryptosporidium* (e.g. North Battleford, SK)

Chemical/Industrial Contaminants

- chlorination by-products (e.g. chloroform can cause cancer at high levels)
- volatile organic compounds, heavy metals, pesticides and other industrial waste products can be present in groundwater
- fluoride at high levels (greater than that of municipal fluoridation) can cause skeletal fluorosis

Soil

- contamination sources: rupture of underground storage tanks, use of pesticides and herbicides, percolation of contaminated water runoffs, leaching of wastes from landfills, dust from smelting and coal burning power plants, direct discharge of industrial wastes, lead deposition, leakage of transformers
- most common chemicals: petroleum hydrocarbons, solvents, lead, pesticides, motor oil, other industrial waste products
- health effects:
 - infants and toddlers at highest risk of exposure
 - dependent on contaminant: leukemia, kidney damage, liver toxicity, neuromuscular blockade, developmental damage to the brain and nervous system, skin rash, eye irritation, headache, nausea, fatigue
- biological contamination: tetanus, *pseudomonas*



BPA, the Toxin of 2009

Bisphenol A (BPA) is a chemical compound found in some hard, clear, lightweight plastics and resins. According to the NIH, animal studies suggest that ingested BPA may imitate estrogen and other hormones. In October 2008, Canada became the first country in the world to ban the import and sale of polycarbonate baby bottles containing BPA, stating that although exposure levels are below levels that cause negative effects, current safety margins need to be higher. The US FDA does not consider normal exposure to BPA to be a hazard, however the NIH has some concern that fetuses, infants and children exposed to BPA may be at increased risk for early-onset puberty, prostate, and breast cancer.



To Fluoridate or Not

At the recommended concentration of 0.8-1.0 mg/L, fluoride reduces cavities by 18-40%, and there is little risk of fluorosis unless other exposures (e.g. toothpaste, rinses, mouthwash, etc.) are swallowed. Opposition raises concerns that the intake is not easily controlled, and that children, small individuals, and others may be more susceptible to health problems. However, public health experts strongly support fluoridation as an effective measure to prevent dental caries at the community level.



Honey and Botulism

Although exceedingly rare, infant botulism has been documented as a form of food poisoning from *C. botulinum* found in honey. When an infant swallows spores of this bacterium, they grow and produce a toxin in the baby's intestine. By the time an infant is 1, its gut has a healthy colony of "good" bacteria that prevents this from occurring.

Food

Table 3. Comparison of Select Biological Contaminants and Effects on Human Health

	Source	Effects
<i>Salmonella</i>	Raw eggs, poultry, meat	GI symptoms
<i>Campylobacter</i>	Raw poultry, raw milk	Joint pain, GI symptoms
<i>Escherichia coli</i>	Various including meat, sprouts Primarily undercooked hamburger meat	Watery or bloody diarrhea Hemolytic uremic syndrome (esp. children)
<i>Listeria monocytogenes</i>	Unpasteurized cheeses, prepared salads, cold cuts	Listeriosis: nausea, vomiting, fever, headache, rarely meningitis or encephalitis
<i>Clostridium botulinum</i>	Unpasteurized honey, canned foods	Dizziness, weakness, respiratory failure, GI symptoms: thirst, nausea, constipation
Prion (BSE)	Beef and beef products	Creutzfeldt-Jakob disease

BSE = bovine spongiform encephalopathy

- other biological food contaminants include:
 - viruses
 - mould toxins (e.g. aflatoxin → liver cancer)
 - parasites (e.g. toxoplasmosis, tapeworm)
 - paralytic and shellfish poisoning (rare)
 - genetically modified organisms (GMO) – controversial

Chemical Contaminants

- many persistent organic pollutants are fat-soluble so they "bio-accumulate" with increasing amount of the contaminant in organisms higher up the food chain
- drugs (antibiotics, hormones)
 - emerging field of study, organic pollutants can have hormonal effects and cause endocrine disruption
- inadequately prepared herbal medications
- food additives and preservatives
 - nitrites can be converted to carcinogenic nitrosamines; highest in cured meats
 - sulphites commonly used as preservatives; associated with sulphite allergy (hives, nausea, shock) rarely
- pesticide residues
 - older pesticides (e.g. DDT) have considerable human health effects
 - many older pesticides still being used in countries where restrictions are less strict than in Canada
 - current debate about DDT use in malaria-endemic countries, weighing risks of DDT vs. risks of malaria
- polychlorinated biphenyls (PCBs)
 - levels continue to increase in the Arctic
 - effects (severe acne, numbness, muscle spasm, bronchitis) much more likely to be seen in occupationally exposed individuals than in the general population
- dioxins and furans
 - levels highest in fish and marine mammals, also present in breast milk
 - can cause immunosuppression, liver disease, respiratory disease

Heavy Metal Toxicity

Background

- 100+ elements, 80 are metals, <30 have described toxic effects
- exposure may be acute or chronic, local or systemic
- after exposure, superabundant metals bind to proteins, changing their enzymatic activity, leading to diffuse disease manifestations

At-risk Groups

- children: hand-to-mouth, incomplete blood brain barrier
- pregnant women and developing fetus: heavy metals cross placenta; mothers release heavy metal stores at times of calcium stress
- adults (higher threshold): occupational, developing countries, hobbies

Etiology

- iatrogenic (e.g. gold treatment for RA, lithium treatment for BAD)
- inhalation (e.g. zinc oxide, lead gasoline fumes)
- ingestion (e.g. lead paint, mercury in fish, folk remedies)
- industry (e.g. methyl mercury industrial spill caused Minamata disease)

Treatment

- generalized workup – symptoms are usually wide-ranging and non-specific
- chelation therapy (e.g. dimercaprol)

Occupational Health

- occupational health is the maintenance and promotion of health in the work environment
- 920 workplace fatalities (more deaths than due to HIV/AIDS) and 373,216 lost time injuries in Canada in 2001
- 5,703 fatal work injuries in the United States in 2006; rate = 3.9 per 100,000 workers
- occupational health services include physicians, nurses, engineers, ergonomists, safety officers, physicists, technicians and others
- services encompass health promotion and protection (primary prevention), disease prevention (secondary prevention) and treatment and rehabilitation (tertiary prevention)
- general bias towards reporting occupational injuries versus occupational disease, as occupational disease is harder to identify

Health Promotion and Protection

- take action in the workplace so the worker is protected from injury or illness
 - identifying workplace hazards [e.g. through material safety data sheets (MSDS)]
 - assessing risk
 - reducing exposure
 - ♦ **source:** substituting a less toxic chemical
 - ♦ **path:** enclosing a source of noise in a sound-proof room
 - ♦ **worker:** personal protection equipment (e.g. reflective vests, helmets)
 - ♦ **worker education** (e.g. emergency protocols, material safety education)
 - ♦ **rotation of workers:** decrease exposure for each worker but more workers exposed



- Reducing Exposure in the Workplace**
- Engineering controls – most preferred
 - Administrative/work practices
 - Personal protective equipment – least preferred due to compliance issues

Disease Prevention

- monitor workers' health to prevent the development of disease
 - periodic examinations to facilitate pre-symptomatic diagnosis (e.g. screening for lead exposure); substance abuse screening where performance impairment is suspected

Treatment and Rehabilitation

- treat injury or illness with safe return to the workplace
- may require rehabilitation, retraining, change in job duties, and/or workers' compensation

Legislation

- universal across Canada for corporate responsibility in the workplace: due diligence, application of Workplace Hazardous Materials Information System (WHMIS), existence of joint health and safety committees in the workplace with representatives from workers and management
- jurisdiction in Canada is provincial (90% of Canadian workers), except for 16 federally regulated industries (e.g. airports, banks, highway transport) under the *Canada Labour Code*
- Ontario's *Occupational Health and Safety Act*
 - sets out rights of workers and duties of employers, procedures for dealing with workplace hazards and law enforcement
 - workers have the right to
 - ♦ **participate** (e.g. have representatives on joint health and safety committees)
 - ♦ **know** (e.g. be trained and have information about workplace hazards)
 - ♦ **refuse work** (e.g. workers can decline tasks they feel are overly dangerous)
 - ♦ **stop work** (e.g. 'certified' workers can halt work they feel is dangerous to other workers)
 - employers must take precautions to protect the health and safety of employees and investigate concerns
 - enforced by Ministry of Labour via inspectors
- **Health Protection and Promotion Act (HPPA)**
 - Medical Officer of Health has right to investigate and manage health hazards where workplace exposures may impact non-workers (e.g. community members living close to the work site)

Ontario's Workplace Safety and Insurance Act

- establishes Workplace Safety and Insurance Board (WSIB), an autonomous government agency which oversees workplace safety training and administers insurance for workers and employers (previously Workers' Compensation Board, WCB)
- WSIB decides benefits for workers, which may include reimbursement for
 - loss of earned income
 - non-economic loss (e.g. physical, functional or psychological loss extending beyond the workplace)
 - loss of retirement income
 - health care expenses (e.g. first-aid, medical treatment)
 - survivor benefits (e.g. dependents and spouses can receive benefits)
- employers pay for costs (e.g. no government funding)
- no-fault insurance (e.g. worker has no right to sue the employer) in return for guaranteed compensation for accepted claims
- negligence is not considered a factor
- physicians are required to provide the WSIB with information about a worker's health without a medical waiver once a claim is made

Taking an Occupational Health History

- work description including occupational profile
- prior or current exposure to dusts, chemicals, solvents, radiation, biological agents, loud noise, mechanical or psychosocial stressors
- review of relevant workplace material safety data sheets (ask patient to provide these)
- look for symptoms of disease and job-related injuries
- temporal relationship between symptoms and exposure
- description of other environments (home, neighbourhood)
- hobbies
- occupation of family members

Occupational Hazards

Physical

- general trauma: fractures, lacerations
- noise (e.g. hearing loss)
- temperature (e.g. heat cramps, heat exhaustion, heat stroke)
- air pressure (e.g. barotraumas, decompression sickness)
- ergonomic
 - repetitive use/overuse injuries, excessive force, awkward postures, poorly designed physical work environment
 - may cause tenosynovitis, bursitis, carpal tunnel syndrome
- radiation
 - non-ionizing: visible light, infrared (DNA strand breakage from sunlight, burns)
 - ionizing: UV, x-rays, gamma rays, etc.
- electricity

Chemical

- organic solvents (e.g. benzene, methyl alcohol; most toxic is carbon tetrachloride)
- mineral dusts (e.g. silica leads to silicosis and predisposition to TB, asbestos leads to diffuse fibrosis and mesothelioma, coal leads to pneumoconiosis)
- heavy metals (e.g. nickel, cadmium, mercury, lead)
 - lead is ubiquitous and can cause severe disability
- gases (halogen gases, sulphur dioxide, carbon monoxide, silo filler's disease)
- second hand smoke – causal factor for lung cancer, lung disease, heart disease, asthma exacerbations; may be linked to miscarriage
 - exposure restricted in most municipal, provincial, and federal jurisdictions
- skin diseases are the major portion of compensations (e.g. contact dermatitis, occupational acne, pigmentation disorders)

Biological

- exposure to bacteria, viruses, fungi, protozoa, *Rickettsia*
- blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)
- consider exposure to disease endemic countries, travelers from endemic countries, or recent travel history in the setting of acute onset of symptoms (e.g. SARS, TB)

Psychosocial Stresses

- due to workload, responsibility, fear of job loss, geographical isolation, shift work, harassment (sexual/non-sexual)
- incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)

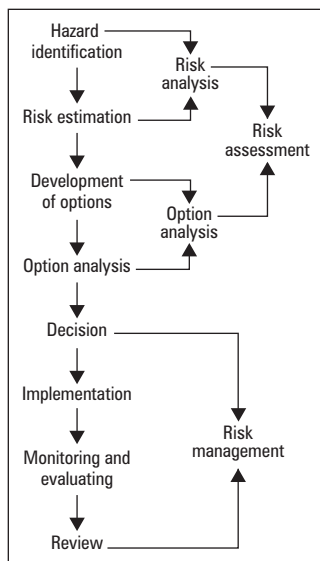


Figure 13. Risk Assessment and Management

Appendix 1. Reportable Diseases

As part of the health system, physicians are required by law to report certain diseases to public health for the following reasons

1. to control the outbreak
 - if the disease presents the threat of an outbreak (e.g. measles, salmonella, respiratory diseases in institutions)
2. to prevent spread
 - if the disease presents a significant threat to individuals or a subset of the population (e.g. Lassa fever)
3. for surveillance
 - if the disease is preventable with immunization (e.g. polio, diphtheria, congenital rubella)
4. if individuals infected require education, treatment and/or partner notification (e.g. gonorrhea, TB)

Physicians should also report unlisted diseases that appear in clusters.

The following list is based on the reportable diseases in Ontario for 2009.

Source: *Health Protection and Promotion Act*, O. Reg. 559/91, amended to O. Reg. 49/07.

Acquired Immunodeficiency Syndrome (AIDS)	Hantavirus pulmonary syndrome	Q Fever
Amebiasis	Hemorrhagic fevers, including,	Rabies
Anthrax	i. Ebola virus disease	Respiratory infection outbreaks in institutions
Botulism	ii. Marburg virus disease	Rubella
Brucellosis	iii. Other viral causes	Rubella, congenital syndrome
Campylobacter enteritis	Hepatitis, viral,	Salmonellosis
Chancroid	i. Hepatitis A	Severe Acute Respiratory Syndrome (SARS)
Chickenpox (Varicella)	ii. Hepatitis B	Shigellosis
<i>Chlamydia trachomatis</i> infections	iii. Hepatitis C	Smallpox
Cholera	iv. Hepatitis D (Delta hepatitis)	Syphilis
Cryptosporidiosis	Herpes, neonatal	
Cyclosporiasis	Influenza	Tetanus
Cytomegalovirus infection, congenital	Lassa Fever	Transmissible Spongiform Encephalopathy, including:
Diphtheria	Legionellosis	i. Creutzfeldt-Jakob Disease, all types
Encephalitis, including,	Leprosy	ii. Gerstmann-Sträussler-Scheinker Syndrome
i. Primary, viral	Listeriosis	iii. Fatal Familial Insomnia
ii. Post-infectious	Lyme Disease	iv. Kuru
iii. Vaccine-related	Malaria	Trichinosis
iv. Subacute sclerosing panencephalitis	Measles	Tuberculosis
v. Unspecified	Meningitis, acute,	Tularemia
Food poisoning, all causes	i. Bacterial	Typhoid Fever
Gastroenteritis, institutional outbreaks	ii. Viral	
Giardiasis, except asymptomatic cases	iii. Other	Verotoxin-producing <i>E. coli</i> infection indicator conditions, including Hemolytic Uremic Syndrome (HUS)
Gonorrhea	Meningococcal disease, invasive	West Nile Virus illness
Group A Streptococcal disease, invasive	Mumps	Yellow Fever
Group B Streptococcal disease, neonatal	Ophthalmia neonatorum	Yersiniosis
<i>Haemophilus influenzae b</i> disease, invasive	Paratyphoid Fever	
	Pertussis (Whooping Cough)	
	Plague	
	Pneumococcal disease, invasive	
	Poliomyelitis, acute	
	Psittacosis/Ornithosis	

Appendix 2. Global Health Statistics

Region	Country	Demographics		Healthcare Resources and Spending						Mortality and Burden of Disease				
		Gross National Income per Capita (PPP intl. \$)	Population Annual Growth Rate (%)	Healthcare Resources (density per 10,000 population)		Per Capita health Expenditures		Life Expectancy (years)		Mortality Rate (per 1000 live births)		Years of Life Lost to (%)		
				Hospital Beds	Nurses and Midwives	Physicians	(PPP intl. \$)	2005	2005	(US\$)	Total	Healthy	Infant	Under-5
		2006	2006	2000-2006	1998-2006	1997-2006	2005	2005	2005	2003	2006	2006	2006	2006
Sub-Saharan Africa	Congo, DR	270	3.2	11	5	1	17	5	47	37	129	205	82	11
	Kenya	1470	2.6	14	12	1	95	24	53	44	79	121	81	8
	Nigeria	1410	2.4	5	17	3	45	27	48	42	99	191	83	7
	Sierra Leone	610	2.8	4	5	<1.0	41	8	40	29	159	269	86	8
	Uganda	880	3.2	11	7	<1.0	130	22	50	43	78	134	84	8
Americas	Argentina	11670	1	41	8	30	1529	484	75	65	14	17	18	17
	Bolivia	3810	1.9	11	21	12	206	73	66	54	50	61	55	11
	Canada	36280	0.9	34	101	19	3452	3463	81	72	5	6	6	15
	Cuba	1070	0.1	49	74	59	333	310	78	68	5	7	10	17
	Haiti	7050	1.6	8	1	3	71	28	61	44	60	80	84	2
	Jamaica	11990	0.6	17	17	9	210	170	72	65	26	32	30	4
	Mexico	44070	1	10	9	20	725	474	74	65	29	35	27	19
	U.S.A		1	32	94	26	6347	6347	78	69	7	8	9	17
	Egypt	4940	1.8	22	34	24	279	78	68	59	29	35	32	8
	Pakistan	2410	1.8	12	5	8	49	15	63	53	78	97	70	8
E. Mediterranean	Tunisia	6490	1.1	19	29	13	477	158	72	62	19	23	18	19
	France	32240	0.6	73	80	34	3406	3926	81	72	4	5	6	16
Europe	Germany	32680	0	83	80	34	3250	3628	80	72	4	5	5	10
	Norway	50070	0.6	41	162	38	4331	5942	80	72	3	4	5	12
	Russia	12740	-0.5	97	85	43	561	277	66	58	10	13	8	28
	U.K.	33650	0.4	39	128	23	2598	3065	79	71	5	6	10	9
	India	2460	1.5		13	6	100	36	63	53	57	76	58	13
SE Asia	Thailand	7440	0.7		28	4	323	98	72	60	7	8	43	17
	Australia	33940	1.1	40	97	25	3001	3181	82	73	5	6	5	17
Western Pacific	China	4660	0.6	22	10	14	315	81	73	64	20	24	23	21
	Japan	32840	0	141	95	21	2474	2908	83	75	3	4	8	16

References

Journals

Bradford-Hill A – “The Environment and Disease: Association or Causation?” *Proc. Royal Soc. Med.* 1966;58: 295.
Kass NE. An ethics framework for public health. *Am J Public Health* 2001;91:1776-1782.

Government Resources

Hamilton N, and T. Bhatti. Integrated model of population health and health promotion. Ottawa: Health promotion and programs branch; 1996.
Canadian Public Health Association and WHO. Ottawa Charter for Health Promotion. Ottawa: Health and Welfare Canada, 1986.
Health Canada. Health and environment: partners for life. Ottawa: Minister of Public Works and Government Services Canada; 1997.
Health Protection and Promotion Act, R.S.O. 1990, c. H.7.
Health Protection and Promotion Act, R.S.O. 1990., c.H.7; O. Reg. 559/91, amended to O. Reg. 49/07.

Textbooks

Hennekens, C. Buring J. Epidemiology in medicine. Philadelphia: Lippincott, Williams & Wilkins, 1987.
Hully SB and Cummings SR. Designing clinical research: an epidemiologic approach. Baltimore: Williams & Wilkins, 1988.
Kelsey JL et al. Methods in Observational Epidemiology, Second Edition. Oxford University Press, 1996.
Last JM. A Dictionary of Epidemiology. 4th e.d. Oxford University Press, 2001.
Sackett DL, Strauss SE, Richardson WS, Rosenberg W and Haynes RB. Evidence-Based Medicine: How to practice and teach EBM. 2nd ed. Toronto: Churchill, Livingstone, 2002.
Shah CP. Public health and preventive medicine in Canada. 4th ed. Toronto: University of Toronto Press, 1998.
Shah CP. Public health and preventive medicine in Canada. 5th ed. Toronto: Elsevier Canada, 2003.

Websites

Association of Workers' Compensation Boards of Canada www.avcbc.org
Bureau of Labour Statistics www.bls.gov
Canada's National Occupational Health and Safety www.canoshweb.org
Canadian Centre for Occupational Health and Safety www.ccohs.ca
Canadian Food Inspection Agency www.inspection.gc.ca/english/agen/agene.shtml
Canadian Institute for Health Information www.cihi.ca
Canadian Medical Association www.cma.ca
Canadian Public Health Association www.cpha.ca
Canadian Society for International Health www.csih.org
Canadian Task Force on Preventative Health Care www.ctfphc.org
Center for Disease Control and Prevention www.cdc.gov
Health Canada www.hc-sc.gc.ca
Institute for Population and Public Health, Canadian Institutes for Health Research www.cihr-irsc.gc.ca/e/13970.html
Intergovernmental Panel on Climate Change www.ipcc.ch
Medical Council of Canada www.mcc.ca
MedTerms www.medterms.com
National Advisory Committee on Immunization www.phac-aspc.gc.ca/naci-ccni/
Ontario Ministry of Labour Occupational Health and Safety www.gov.on.ca/LAB/ohs
Pan-American Health Organization www.paho.org
Public Health Agency of Canada www.phac-aspc.gc.ca/about_apropos/index/html
WHO, World Health Report 2006 www.who.int/whr/2006/en/index.html
Workplace Safety and Insurance Board www.wsib.on.ca
World Bank www.worldbank.org

Evidence-Based Medicine Resources

Up-to-Date www.uptodate.com
Clinical Evidence www.clinicalevidence.com
Pier (ACP) pier.acponline.org
OVID EBM Reviews gateway.ovid.com/ovidweb.cgi
PubMed – Clinical Queries www.pubmed.com
BMJ Updates bmjupdates.mcmaster.ca
Users' Guide Series www.cche.net/usersguides/main.asp

Notes

Lined area for taking notes.

Jacqui Holiff, Melinda White and Karen-Rose Wilson, chapter editors

Christopher Kitamura and Michelle Lam, associate editors

Janine Hutson, EBM editor

Dr. Jodi Lofchy and Dr. John Teshima, staff editors

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Psychiatric Assessment

History



Screening Questions for Major Psychiatric Disorders

- Have you been feeling down, depressed or hopeless?
- Do you feel anxious or worry about things?
- Has there been a time in your life where you have felt euphoric, extremely talkative and had a lot of energy and a decreased need for sleep?
- Do you see or hear things that you think other people cannot?
- Have you ever thought of harming yourself or committing suicide?



Psychiatric Functional Inquiry

MOAPS

- Mood
- Organic (e.g. substances)
- Anxiety
- Psychosis
- Safety



The MSE is analogous to the physical exam. It focuses on current signs, symptoms, affect, behaviour and cognition.



Mental Status Exam

ASEPTIC

- Appearance and behaviour
- Speech
- Emotion (mood and affect)
- Perception
- Thought content and process
- Insight and judgment
- Cognition

Identifying Data

- name, sex, age, ethnicity, marital status, religion, occupation, education, living situation, referral source

Reliability of Patient as a Historian

- may need collateral source (e.g. parent, teacher) if patient unable/unwilling to co-operate

Chief Complaint

- in patient's own words
- duration, previous history of disorder or treatment

History of Present Illness

- reason for seeking help (that day), current symptoms (onset, duration and course), stressors, supports, functional status, relevant associated symptoms (pertinent positives and negatives)
- safety screen: Is the patient endangering self or others? Dependents at home (e.g. children, pets), ability to drive safely, ability to care for self (e.g. eating, hygiene, taking medications)

Psychiatric Functional Inquiry

- mood: depressed, manic
- anxiety: worries, obsessions, compulsions, panic attacks, phobias
- psychosis: hallucinations, delusions, thought form disorders
- suicide/homicide: ideation, plan, intent, history of attempts
- organic: EtOH/drug use or withdrawal, illness, dementia

Past Psychiatric History

- all previous psychiatric diagnoses, psychiatric contacts, treatments (pharmacological and non-pharmacological) and hospitalizations
- also include past suicide attempts, substance use/abuse, and legal problems

Past Medical/Surgical History

- all medical, surgical, neurological (e.g. head trauma, seizures), and psychosomatic illnesses
- medications, allergies

Family Psychiatric/Medical History

- family members: ages, occupations, personalities, medical or genetic illnesses and treatments, relationships with parents/siblings
- family psychiatric history: any past or current psychiatric illnesses and hospitalizations, suicide, depression, substance abuse, history of "nervous breakdown/bad nerves," forensic history, any past treatment by psychiatrist or other therapist

Past Personal History

- prenatal and perinatal history (desired vs. unwanted pregnancy, maternal and fetal health, domestic violence, maternal substance use, complications of pregnancy/delivery)
- early childhood to age 3 (developmental milestones, activity/attention level, family stability, attachment figures)
- middle childhood to age 11 (school performance, peer relationships, fire-setting, stealing, incontinence)
- late childhood to adolescence (drug/alcohol, legal problems, peer and family relationships)
- adulthood (education, occupations, relationships)
- psychosexual history (paraphilias, gender roles, sexual abuse, sexual dysfunction)
- personality before current illness, recent changes in personality

Mental Status Exam (MSE)

General Appearance and Behaviour

- dress, grooming, posture, gait, physical characteristics, body habitus, apparent vs. chronological age, facial expression (e.g. sad, suspicious)
- psychomotor activity (agitation, retardation), abnormal movements or lack thereof (tremors, akathisia, tardive dyskinesia, paralysis), attention level and eye contact, attitude toward examiner (ability to interact, level of co-operation)

Speech

- rate (e.g. pressured, slowed), rhythm/fluency, volume, tone, articulation, quantity, spontaneity

Mood and Affect

- mood – subjective emotional state; in patient's own words
- affect – objective emotional state; inferred from emotional responses to stimuli, described in terms of:
 - quality (euthymic, depressed, elevated, anxious)
 - range (full, restricted, flat, blunted)
 - stability (fixed, labile)
 - mood congruence (inferred by reader by comparing mood and affect descriptions)
 - appropriateness to thought content

Thought Process

- coherence – coherent, incoherent
- logic – logical, illogical
- stream
 - goal-directed
 - circumstantial – speech that is indirect and delayed in reaching its goal; eventually comes back to the point
 - tangential – speech is oblique or irrelevant; does not come back to the original point
 - loosening of associations – illogical shifting between topics
 - flight of ideas – quickly skipping from one idea to another where the ideas are marginally connected, associated with mania
 - word salad – jumble of words lacking meaning or logical coherence
- perseveration – repetition of the same verbal or motor response to stimuli
- echolalia – repetition of phrases or words spoken by someone else
- thought blocking – sudden cessation of flow of thought and speech
- clang associations – speech based on sound such as rhyming or punning
- neologism – use of novel words or of existing words in a novel fashion

Thought Content

- suicidal ideation/homicidal ideation
 - low – fleeting thoughts, no formulated plan, no intent
 - intermediate – more frequent ideation, well formulated plan, no active intent
 - high – persistent ideation and profound hopelessness/anger, well formulated plan, active intent, believes suicide/homicide is the only helpful option available
- pre-occupations, ruminations – reflections/thoughts at length, not fixed or false
- obsession – recurrent and persistent thought, impulse or image which is intrusive or inappropriate
 - cannot be stopped by logic or reason
 - causes marked anxiety and distress
 - common themes – contamination, orderliness, sexual, pathological doubt/worry/guilt
- magical thinking – belief that thinking something will make it happen; normal in kids
- ideas of reference – similar to delusion of reference but the reality of the belief is questioned
- overvalued ideas – unusual/odd beliefs that are not of delusional proportions
- first rank symptoms of schizophrenia – thought insertion/withdrawal/broadcasting
- delusion – a fixed false belief that is out of keeping with a person's cultural or religious background and is firmly held despite incontrovertible proof to the contrary
- progression of increasing pathology, decreasing insight: ideas/themes < preoccupations < ruminations < obsessions < magical thinking < ideas of reference < overvalued ideas < first rank symptoms < delusions

Perception

- hallucination – sensory perception in the absence of external stimuli that is similar in quality to a true perception, auditory (most common), visual, gustatory, olfactory, tactile
- illusion – misperception of a real external stimulus
- depersonalization – change in self-awareness such that the person feels unreal, detached from his or her body, and/or unable to feel emotion
- derealization – feeling that the world/outer environment is unreal

Cognition

- level of consciousness
- orientation – time, place, person
- memory – immediate, recent, remote
- global evaluation of intellect (below average, average, above average)
- intellectual functions – attention, concentration, calculation, abstraction (proverb interpretation, similarities test), language, communication

Insight

- patient's ability to realize that he or she has a physical or mental illness and to understand its implications

Judgment

- ability to understand relationships between facts and draw conclusions that determine one's actions



Spectrum of Affect

Full > Restricted > Blunted > Flat



There is poor correlation between clinical impression of suicide risk and frequency of attempts.



Delusions

- Persecutory – belief that others are trying to cause harm
- Delusions of reference – interpreting publicly known events/celebrities as having direct reference to the patient
- Erotomania – belief that another is in love with you
- Grandiose – belief of an inflated sense of self-worth or power
- Religious – belief of receiving instructions/powers from a higher being; of being a higher being
- Somatic – belief that one has a physical disorder/defect
- Nihilistic – belief that things do not exist; a sense that everything is unreal



Cognitive Assessment

Use Folstein Mini Mental State Exam (MMSE) to assess:

- Orientation (time and place)
- Memory (immediate and delayed recall)
- Attention and Concentration
- Language (comprehension, reading, writing, repetition, naming)
- Spatial ability (intersecting pentagons)

Gross screen for cognitive dysfunction: Total score is out of 30; <24 abnormal 20-24 mild, 10-19 moderate, <10 severe



Assessing Insight and Judgment

Insight

- Do you think that you have a mental illness?
- Why are you taking this medication?
- Why are you in the hospital?

Judgment

Can be observed from collected history and patient's appearance and actions.

- Is he/she dressed appropriately for the weather?
- Is he/she acting appropriately in the given situation?
- Is he/she taking care of self and/or dependents?



Axis V: Global Assessment of Functioning

91-100	Superior functioning in a wide range of activities
81-90	Absent or minimal symptoms
71-80	If symptoms are present, they are transient and expected reactions to psychosocial stressors
61-70	Some mild symptoms or some difficulty but generally functioning well
51-60	Moderate symptoms or difficulty
41-50	Serious symptoms or difficulty
31-40	Some impairment in reality testing/communication, impairment in several areas
21-30	Behaviour is influenced by delusions/hallucinations or serious impairment in communication/judgment
11-20	Some danger of hurting self or others or occasionally fails to maintain minimal hygiene or gross impairment in communication
1-10	Persistent danger of severely hurting self or others or persistent inability to maintain minimal personal hygiene or serious suicidal act
0	Inadequate information



Summary of Axes

Multiaxial Assessment

- **Axis I**
 - differential diagnosis of DSM-IV clinical disorders
- **Axis II**
 - personality disorders, developmental disability
- **Axis III**
 - general medical conditions that are potentially relevant to the understanding or management of the mental disorder
- **Axis IV**
 - psychosocial and environmental issues
- **Axis V**
 - global assessment of functioning (GAF, 0 to 100) incorporating effects of axes I to IV

Formulation

- a diagram outlining current issues and interrelations between an individual's biological, psychological, and social factors
- for each category: predisposing, precipitating, perpetuating, and protecting factors

Approach to Management

1. biological (e.g. pharmacotherapy)
2. psychological (e.g. CBT)
3. social (e.g. support group)

Psychotic Disorders

Definition

- characterized by a significant impairment in reality testing
 - delusions or hallucinations (with/without insight into their pathological nature)
 - behaviour so disorganized that it is reasonable to infer that reality testing is disturbed

Differential Diagnosis of Psychosis

- primary psychotic disorders: schizophrenia, schizophreniform, brief psychotic, schizoaffective, delusional disorder
- mood disorders: depression with psychotic features, bipolar disorder (manic episode with psychotic features)
- personality disorders: schizotypal, schizoid, borderline, paranoid, obsessive-compulsive
- general medical conditions: tumour, head trauma, dementia, delirium, metabolic
- substance-induced psychosis: intoxication or withdrawal

Schizophrenia

DSM-IV-TR Diagnostic Criteria for Schizophrenia

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- characteristic symptoms (active phase): ≥ 2 of the following, each present for a significant portion of time during a **1-month period** (or less if successfully treated)
 - delusions
 - hallucinations
 - disorganized speech (e.g. frequent derailment or incoherence)
 - grossly disorganized or catatonic behaviour
 - negative symptoms, e.g. affective flattening, alogia (inability to speak), or avolition (inability to initiate and persist in goal-directed activities)
- only 1 "A" symptom is required if delusions are bizarre or hallucinations consist of a voice keeping a running commentary on the person's behaviour or thoughts, or 2 or more voices conversing with each other
- social/occupational dysfunction: ≥ 1 major areas of functioning (work, interpersonal relations, self-care) markedly below the level achieved prior to the onset of symptoms
- continuous signs of disturbance for ≥ 6 months, including ≥ 1 month of active phase symptoms; may include prodromal or residual phases
- schizoaffective and mood disorders excluded
- the disturbance is not due to the direct physiological effects of a substance or a general medical condition (GMC)
- if history of pervasive developmental disorder, additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month



Differential Diagnosis of Psychosis

GASPP

General medical condition
Affective disorders
Substance induced
Psychotic disorders
Personality disorders



Management of Acute Psychosis and Mania

- Ensure safety of self, patient and other patients
- Have an exit strategy
- Decrease stimulation
- Assume a non-threatening stance
- IM medications (benzodiazepine + antipsychotic) often needed as patient may refuse oral meds
- Physical restraints may be necessary
- Do not use antidepressants or stimulants

Subtypes

- paranoid
 - preoccupation with one or more delusions (typically persecutory or grandiose) or frequent auditory hallucinations
 - relative preservation of cognitive functioning and affect; onset tends to be later in life; believed to have the best prognosis
- catatonic
 - at least two of: motor immobility (catalepsy or stupor); excessive motor activity (purposeless, not influenced by external stimuli); extreme negativism (resistance to instructions/attempts to be moved) or mutism; peculiar voluntary movement (posturing, stereotyped movements, prominent mannerisms); echolalia (repeating words/phrases of another's speech) or echopraxia (imitative repetition of another's movements, gestures or posture)
- disorganized
 - disorganized speech and behaviour; flat or inappropriate affect
 - poor premorbid personality, early and insidious onset, and continuous course without significant remissions
- undifferentiated
 - symptoms of criteria A met, but does not fall into the 3 previous subtypes
- residual
 - absence of prominent delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour
 - continuing evidence of disturbance indicated by the presence of negative symptoms or two or more symptoms in criteria A present in attenuated form

Epidemiology

- prevalence: 0.5%-1%; M:F = 1:1
- mean age of onset: females ~27; males ~21

Etiology

- multifactorial: disorder is a result of interaction between both biological and environmental factors
 - genetic – 50% concordance in monozygotic (MZ) twins; 40% if both parents have schizophrenia; 10% of dizygotic (DZ) twins, siblings, children affected
 - neurochemistry – “dopamine hypothesis” theory: excess activity in the mesolimbic dopamine pathway may mediate the positive symptoms of psychosis (i.e. delusions, hallucinations, disorganized speech and behaviour, and agitation)
 - neuroanatomy – decreased frontal lobe function, asymmetric temporal/limbic function, decreased basal ganglia function; subtle changes in thalamus, cortex, corpus callosum, and ventricles; cytoarchitectural abnormalities
 - neuroendocrinology – abnormal growth hormone, prolactin, cortisol, and adrenocorticotrophic hormone
 - neuropsychology – global defects seen in attention, language, and memory suggest lack of connectivity of neural networks
 - indirect evidence of geographical variance, winter season of birth, and prenatal viral exposure

Pathophysiology

- neurodegenerative theory
 - natural history may be rapid or gradual decline in function and ability to communicate
 - glutamate system may mediate progressive degeneration by excitotoxic mechanism which leads to production of free radicals
- neurodevelopmental theory: abnormal development of the brain from prenatal life
 - neurons fail to migrate correctly, make inappropriate connections, and break down in later life
 - inappropriate apoptosis during neurodevelopment resulting in faulty connections between neurons

Management of Schizophrenia

- biological
 - acute treatment and maintenance with antipsychotics ± anticonvulsants ± anxiolytics
 - management of side effects
- psychosocial
 - psychotherapy (individual, family, group): supportive, cognitive behavioural therapy (CBT)
 - assertive community treatment (ACT)
 - social skills training, employment programs, disability benefits
 - housing (group home, boarding home, transitional home)

**Suggested Criteria for Prodromal Syndromes**

- Attenuated positive symptom syndrome: Abnormal unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and/or organization of communication; onset or worsening in past year
- Brief intermittent psychotic syndrome: Frankly psychotic, unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and/or organization of communication; onset in past three months
- Genetic risk plus functional deterioration: First-degree relative with history of any psychotic disorder or schizotypal personality disorder in patient; substantial functional decline in past year

Adapted from Sadock, B. J. and Sadock, V. A. Kaplan and Sadock's *Comprehensive Textbook of Psychiatry*, 8th Edition. Lippincott Williams & Wilkins, 2005.

Relationship Between Duration of Untreated Psychosis (DUP) and Outcome in First-episode Schizophrenia

Am J Psychiatry 2005; 162:1785-1804

Purpose: To review the association between DUP and symptom severity at first treatment contact, and between DUP and treatment outcomes.

Study Characteristics: Critical review and meta-analysis of 43 studies with 4177 patients.

Participants: Patients with non-affective psychotic disorders at or close to first treatment.

Results: Shorter DUP was associated with greater response to antipsychotic treatment, as measured by global psychopathology, positive symptoms, negative symptoms, and functional outcomes. At the time of treatment initiation, longer DUP was associated with the severity of negative symptoms but not with the severity of positive symptoms, global psychopathology, or neurocognitive function.

Conclusions: DUP may be a potentially modifiable prognostic factor.

**Supportive Evidence for Dopamine Hypothesis**

- Dopamine (DA) agonists exacerbate schizophrenia
- Antipsychotic drugs act by blocking post-synaptic DA receptors
- Potency of many antipsychotic drugs correlates with D2 blockade of post-synaptic receptors
- Antipsychotic drugs are associated with an increase in the number of D2 and D4 post-synaptic receptors

**Good Prognostic Factors**

- Acute onset
- Precipitating factors
- Good cognitive functioning
- Good premorbid functioning
- No family history
- Presence of affective symptoms
- Absence of structural brain abnormalities
- Good response to drugs
- Good support system

Prognosis

- the majority of individuals display some type of prodromal phase
- course is variable: some individuals have exacerbations and remissions and others remain chronically ill; accurate prediction of the long term outcome is not possible
- early in the illness, negative symptoms may be prominent; positive symptoms appear and typically diminish with treatment; negative symptoms may become more prominent and more disabling
- over time, 1/3 improve, 1/3 remain the same, 1/3 worsen

Schizophreniform Disorder

- **diagnosis:** criteria A, D and E of schizophrenia are met; an episode of the disorder lasts at least **1 month** but less than **6 months**. If the symptoms have extended past 6 months the diagnosis becomes schizophrenia
- **treatment:** similar to acute schizophrenia
- **prognosis:** better than schizophrenia; begins and ends more abruptly; good pre- and post-morbid function

Brief Psychotic Disorder

- **diagnosis:** acute psychosis (presence of 1 or more positive symptoms in criteria A1-4 of schizophrenia) lasting from **1 day to 1 month**, with eventual full return to premorbid level of functioning
- can occur after a stressful event or postpartum (see *Postpartum Mood Disorders*, PS10)
- **treatment:** secure environment, antipsychotics, anxiolytics
- **prognosis:** good, self-limiting, should return to pre-morbid function in about 1 month

Schizoaffective Disorder**DSM-IV-TR Diagnostic Criteria for Schizoaffective Disorder**

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- uninterrupted period of illness during which there is either a major depressive episode (MDE), manic episode, or a mixed episode concurrent with symptoms meeting criteria A for schizophrenia
 - in the same period, delusions or hallucinations for **at least 2 weeks** in the absence of prominent mood symptoms
 - symptoms that meet criteria for a mood episode are present for a substantial portion of total duration of active and residual periods of the illness
 - the disturbance is not due to the direct physiological effects of a substance or GMC
- **treatment:** antipsychotics, mood stabilizers, antidepressants
 - **prognosis:** between that of schizophrenia and of mood disorder

Delusional Disorder**DSM-IV-TR Diagnostic Criteria for Delusional Disorder**

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- non-bizarre delusions for at least **1 month**
 - criterion A for schizophrenia has never been met** (though patient may have tactile or olfactory hallucinations if they are related to the delusional theme)
 - functioning not markedly impaired; behaviour not obviously odd or bizarre
 - if mood episodes occur concurrently with delusions, total duration has been brief relative to duration of the delusional periods
 - the disturbance is not due to the direct physiological effects of a substance or GMC
- **subtypes:** erotomaniac, grandiose, jealous, persecutory, somatic, mixed, unspecified
 - **treatment:** psychotherapy, antipsychotics, antidepressants
 - **prognosis:** chronic, unremitting course but high level of functioning

Shared Psychotic Disorder (Folie à Deux)

- **diagnosis:** delusion that develops in an individual who is in a close relationship with another person who already has a psychotic disorder with prominent delusions; the delusion is similar in content to that of the other person
- **treatment:** separation of the two people results in the disappearance of the delusion in the healthier member; antipsychotics may play a role
- **prognosis:** good



Non-bizarre delusions involve situations that could occur in real life (e.g. being followed, poisoned, loved at a distance).

Table 1. Differentiating Psychotic Disorders

Disorder	Psychotic Symptoms	Duration	Mood Symptoms
Brief psychotic disorder	≥1 positive symptoms of criterion A	<1 month	If present, 2°
Schizophreniform disorder	Criterion A	1-6 months	If present, 2°
Schizophrenia	Criterion A	>6 months	If present, 2°
Schizoaffective disorder	≥2 weeks (with no mood symptoms)	>1 month	Present
Delusional disorder	Non-bizarre delusions, hallucinations	>1 month	If present, 2°
2° to substance intoxication/withdrawal	Criterion A	During intoxication or ≤1 month after withdrawal	Variable
2° to mood disorder	Delusions/hallucinations (mood congruent)	Unspecified	1°



Duration of Time Differentiates the following 3 Psychotic Disorders
 Brief psychotic disorder < 1 month
 Schizophreniform disorder 1-6 months
 Schizophrenia > 6 months

Mood Disorders

Definitions

- mood disorders are defined by the presence of mood episodes
- mood episodes represent a combination of symptoms comprising a predominant mood state that is abnormal in quality or duration, e.g. major depressive, manic, mixed, hypomanic
- types of mood disorders include
 - depressive (major depressive disorder, dysthymia)
 - bipolar (bipolar I/II disorder, cyclothymia)
 - secondary to GMC, substances, medications

Table 2. Secondary Causes of Mood Disorders

Category	Examples
V Vascular	Cardiomyopathy, CHF, MI, CVA
I Infectious	Encephalitis/meningitis, hepatitis, pneumonia, TB, syphilis
N Neoplastic	Pancreatic cancer, carcinoid, pheochromocytoma
D Degenerative	Huntington's disease, multiple sclerosis, tuberous sclerosis, degenerative (vascular, Alzheimer's dementia)
I Intoxication/Drugs/Deficiencies	Antihypertensives, antiparkinsonian, hormones, steroids, antituberculous, interferon, antineoplastic medications, vitamin deficiencies (Wernicke's encephalopathy, beriberi, pellagra, pernicious anemia)
C Congenital	—
A Autoimmune	SLE, polyarteritis nodosa
T Traumatic	—
E Endocrine/Metabolic	Hypothyroidism, hyperthyroidism, hypopituitarism, SIADH, porphyria, Wilson's disease, diabetes

Medical Workup of Mood Disorder

- routine screening
 - physical examination
 - complete blood count
 - thyroid function test
 - electrolytes
 - urinalysis, urine drug screen
- additional screening:
 - neurological consultation
 - chest x-ray
 - electrocardiogram
 - CT scan

Mood Episodes

DSM-IV-TR Criteria for Major Depressive Episode

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- A. ≥5 of the following symptoms have been present during the same **2-week** period and represent a change from previous functioning; at least one of the symptoms is either **1) depressed mood**, or **2) loss of interest or pleasure (anhedonia)**

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations

- depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others
- markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day



Criteria for Depression (≥5)

MSIGECAPS

Mood – depressed
 Sleep – increased/decreased
 Interest – decreased
 Guilt
 Energy – decreased
 Concentration – decreased
 Appetite – increased/decreased
 Psychomotor – agitation/retardation
 Suicidal ideation

- significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day
 - insomnia or hypersomnia nearly every day
 - psychomotor agitation or retardation nearly every day
 - fatigue or loss of energy nearly every day
 - feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
 - diminished ability to think or concentrate, or indecisiveness, nearly every day
 - recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
- B. the symptoms do not meet criteria for a Mixed Episode (see below)
- C. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- D. the symptoms are not due to the direct physiological effects of a substance or a GMC
- E. the symptoms are not better accounted for by bereavement (i.e. after the loss of a loved one); the symptoms persist for longer than 2 months; symptoms are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

DSM-IV-TR Criteria for Manic Episode

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- A. a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting **≥1 week** (or any duration if hospitalization is necessary)
- B. during the period of mood disturbance, **≥3** of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree:
- inflated self-esteem or grandiosity
 - decreased need for sleep (e.g. feels rested after only 3 hours of sleep)
 - more talkative than usual or pressure to keep talking
 - flight of ideas or subjective experience that thoughts are racing
 - distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli)
 - increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
 - excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g. engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
- C. the symptoms do not meet criteria for a Mixed Episode (see below)
- D. the mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features
- E. the symptoms are not due to the direct physiological effects of a substance (e.g. drug of abuse, medication, or other treatment) or a general medical condition (e.g. hyperthyroidism).
- Note:** Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g. medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder



Criteria for Mania (≥3)

GST PAID

Grandiosity

Sleep (decreased need)

Talkative

Pleasurable activities, Painful consequences

Activity

Ideas (flight of)

Distractible



An example of a mixed episode would be manic behaviour, racing thoughts with depressive or nihilistic content.

Mixed Episode

- criterion met for both manic episode and major depressive episode (MDE) nearly every day for 1 week
- criteria D and E of manic episodes are met

Hypomanic Episode

- criterion A of a manic episode is met, but duration is **≥4 days**
- criterion B and E of manic episodes are met
- episode associated with an uncharacteristic decline in functioning that is observable by others
- change in function is **not severe enough** to cause marked impairment in social or occupational functioning or to necessitate hospitalization
- absence of psychotic features

Depressive Disorders

MAJOR DEPRESSIVE DISORDER

DSM-IV-TR Diagnostic Criteria for Major Depressive Disorder (MDD), Single Episode (vs. Recurrent)

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- A. presence of a single Major Depressive Episode (vs. Recurrent, which requires presence of two or more Major Depressive Episodes; to be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a MDE)

- B. the Major Depressive Episode is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder not otherwise specified
- C. there has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode
Note: This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance- or treatment-induced or are due to the direct physiological effects of a general medical condition

Features/Specifiers

- **psychotic** – with hallucinations or delusions
- **chronic** – lasting 2 years or more
- **catatonic** – at least two of: motor immobility; excessive motor activity; extreme negativism or mutism; peculiarities of voluntary movement; echolalia or echopraxia
- **melancholic** – quality of mood is distinctly depressed, mood is worse in the morning, early morning awakening, marked weight loss, excessive guilt, psychomotor retardation
- **atypical** – increased sleep, weight gain, leaden paralysis, rejection hypersensitivity
- **postpartum** (see *Postpartum Mood Disorders*, PS10)
- **seasonal** – pattern of onset at the same time each year (most often in the fall or winter)

Epidemiology

- prevalence: male 5-12%, female 10-25% (M:F = 1:2)
- mean age of onset: ~30 years

Etiology

- biological
 - genetic: 65-75% MZ twins; 14-19% DZ twins
 - neurotransmitter dysfunction at level of synapse (decreased activity of serotonin, norepinephrine, dopamine)
 - secondary to general medical condition
- psychosocial
 - psychodynamic (e.g. low self-esteem)
 - cognitive (e.g. negative thinking)
 - environmental factors (e.g. job loss, diet, bereavement, history of abuse)
 - co-morbid psychiatric diagnoses (e.g. anxiety, substance abuse, mental retardation, dementia, eating disorder)

Risk Factors

- sex: female > male
- age: onset between 25-50 years of age
- family history: depression, alcohol abuse, sociopathy
- childhood experiences: loss of parent before age 11, negative home environment (abuse, neglect)
- personality: insecure, dependent, obsessional
- recent stressors: illness, financial, legal
- postpartum <6 months
- lack of intimate, confiding relationships or social isolation

Depression in the Elderly

- accounts for about 50% of acute psychiatric admissions in the elderly
- affects about 15% of community residents >65 years old
- high suicide risk due to social isolation, chronic medical illness
- suicide peak: males aged 80-90; females aged 50-65
- often present with somatic complaints (e.g. changes in weight, sleep, energy) or anxiety symptoms
- refer to Table 4 to compare with delirium and dementia

Treatment

- biological: antidepressants (see PS45), lithium, antipsychotics, anxiolytics, electroconvulsive therapy (ECT), light therapy
- psychological
 - individual therapy: psychodynamic, interpersonal, cognitive behavioural therapy
 - family therapy
 - group therapy
- social: vocational rehabilitation, social skills training
- experimental: deep brain stimulation, transcranial magnetic stimulation, vagal nerve stimulation

Prognosis

- one year after diagnosis of a MDE without treatment, 40% of individuals still have symptoms that are sufficiently severe to meet criteria for a full MDE, 20% continue to have some symptoms that no longer meet criteria for a MDE, 40% have no mood disorder

Antidepressants for Depression in Medical Illness

Cochrane Database of Systematic Reviews 2010; Issue 3

This systematic review and meta-analysis of 51 RCTs (3603 patients) compared anti-depressants to placebo in patients with a physical disorder (eg. Cancer, MI) who have been diagnosed as depressed (including Major Depression, Adjustment Disorder, and Dysthymia).

Conclusions: Antidepressants, including SSRIs and TCAs, cause a significant improvement in patients with a physical illness, as compared to placebo.

St. John's Wort for Major Depression

Cochrane Database of Sys Rev 2008; Issue 3

Study: Systematic review of trials that were (1) randomized, double-blinded (2) with patients with major depression (3) comparing St. John's wort (hypericum extracts) with placebo or standard antidepressants and (4) included clinical outcomes.

Patients: 5489 patients with major depression.

Outcomes: 1. Effectiveness: treatment response measured by a depression scale 2. Safety: the proportion of patients who dropped out due to adverse effects.

Intervention: St. John's wort vs. placebo; St. John's wort vs. standard antidepressants.

Results: 29 trials, 5489 patients, with 18 comparisons with placebo and 17 with antidepressants. St. John's wort is more effective than placebo (response rate ratio=1.87, 95% CI), and similarly effective as antidepressants (RRR=1.02, 95%CI). Less adverse effects with hypericum extracts. However, the effect size is dependent on the country of origin.

Cognitive Therapy vs. Medications in the Treatment of Moderate to Severe Depression

Arch Gen Psychiatry 2005; 62:409-416

Study: Randomized control trial.

Patients: 240 outpatients with moderate to severe MDD, aged 18-70.

Intervention: 16 weeks of paroxetine with or without augmentation with lithium carbonate or desipramine hydrochloride (n=120) versus cognitive behavioural therapy (n=60). Response up to 8 weeks was controlled by pill placebo (n=60)

Main Outcomes: The Hamilton Depression Rating scale was used to determine response to treatment.

Results: At 8 weeks, 50% (95%CI 41-59%) of patients on medication and 43% (95%CI 31-56%) of patients on CBT had responded in comparison to 25% (95%CI 16-38%) of patients on pill placebo. There was no significant difference between medication and CBT. At 16 weeks, 46% of patients on medication and 40% of patients on CBT achieved remission.

Summary: There is no difference in efficacy between CBT vs. paroxetine in the treatment of moderate to severe depression.

DYSTHYMIA

DSM-IV-TR Diagnostic Criteria for Dysthymic Disorder

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- A. depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for **≥2 years**. **Note:** In children and adolescents, mood can be irritable and duration must be at least 1 year
- B. presence, while depressed, of **≥2** of the following
 - poor appetite or overeating
 - insomnia or hypersomnia
 - low energy or fatigue
 - low self-esteem
 - poor concentration or difficulty making decisions
 - feelings of hopelessness
- C. during the 2-year period (1 year for children or adolescents) of the disturbance, the person has never been without the symptoms in criteria A and B for more than 2 months at a time
- D. no MDE has been present during the first 2 years of the disturbance (1 year for children and adolescents); i.e. the disturbance is not better accounted for by chronic MDD, or MDD in partial remission
- E. there has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode, and criteria have never been met for Cyclothymic Disorder
- F. the disturbance does not occur exclusively during the course of a chronic Psychotic Disorder, such as Schizophrenia or Delusional Disorder
- G. the symptoms are not due to the direct physiological effects of a substance or a GMC
- H. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

Epidemiology

- point prevalence: 3%; life prevalence: 6%; M:F = 1:2-3

Treatment

- psychological
 - principle treatment for dysthymia
 - individual, group, and family therapy
- biological
 - antidepressant therapy (SSRIs/SNRIs) as an outpatient

Postpartum Mood Disorders

Postpartum "Blues"

- transient period of mild depression, mood instability, anxiety, decreased concentration, increased concern over own health and health of baby – considered to be normal emotional changes related to the puerperium
- occurs in 50-80% of mothers; begins 2-4 days postpartum, usually lasts 48 hours, can last up to 10 days
- does not require psychotropic medication
- patient at increased risk of developing postpartum depression

Postpartum Depression (PPD)

- **diagnosis:** MDE, onset within 4 weeks postpartum
- **clinical presentation**
 - typically lasts 2 to 6 months; residual symptoms can last up to 1 year
 - may present with **psychosis** – rare (0.2%), usually associated with mania, but can be MDE
 - severe symptoms include extreme disinterest in baby, suicidal and infanticidal ideation
- **epidemiology:** occurs in 10% of mothers, risk of recurrence 50%
- **risk factors**
 - previous history of a mood disorder (postpartum or otherwise)
 - psychosocial factors: stressful life events, unemployment, marital conflict, lack of social support, unwanted pregnancy, colicky or sick infant
- **treatment**
 - psychotherapy
 - short-term safety of maternal SSRIs for breastfeeding infants established; long-term effects unknown
 - supportive, non-directive counselling by trained home visitors
 - if depression severe, consider ECT
- **prognosis:** impact on child development – increased risk of cognitive delay, insecure attachment, behavioural disorders; treatment of mother improves outcome for child at 8 months through increased mother-child interaction

Health Canada Advises of Potential Adverse Effects of SSRIs and Other Antidepressants on Newborns

August 9, 2004

Health Canada was concerned that newborns exposed to SSRIs and other antidepressants during the third trimester of pregnancy may be adversely affected, because of reports of complications at birth requiring longer hospitalization, breathing support and tube feeding. Advisory applied to: bupropion (used for depression or smoking cessation), citalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline and venlafaxine. **Conclusions:** Physicians and patients should carefully consider risks, benefits and options for both the mother and unborn baby when treating depression in pregnant women. Consider tapering in the third trimester. Women should consult their doctors before stopping these medications.

Premenstrual Dysphoric Disorder (PMDD)

DSM-IV-TR Diagnostic Criteria for Premenstrual Dysphoric Disorder

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- A. in most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week post-menses, with at least one of the symptoms being one of the first four listed
1. markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
 2. marked anxiety, tension, feeling of being “keyed up” or “on edge”
 3. marked affective lability
 4. persistent and marked anger, irritability, or increased interpersonal conflicts
 5. decreased interest in usual activities
 6. difficulty concentrating
 7. lethargy, easily fatigued, lack of energy
 8. change in appetite – overeating or specific food cravings
 9. hypersomnia or insomnia
 10. a sense of being overwhelmed or out of control
 11. physical symptoms – breast tenderness or swelling, headaches, joint or muscle pain, sensation of bloating or weight gain
- B. the disturbance markedly interferes with work, school, social activities or relationships with others
- C. the disturbance is not merely an exacerbation of the symptoms of another disorder such as Major Depressive Disorder, Panic Disorder, Dysthymic Disorder or Personality Disorder
- D. Criteria A, B and C must be confirmed by prospective daily recordings and/or ratings during at least two consecutive symptomatic cycles

Treatment

- 1st line: SSRIs highly effective in treating PMDD
 - fluoxetine and sertraline most studied
 - can be used intermittently in luteal phase x 14 days
- 2nd line
 - clomipramine
 - alprazolam (Xanax®) for anxiety symptoms
- 3rd line
 - OCP containing progesterone drospirenone (e.g. Yasmin®)
 - GnRH agonists (e.g. leuprolide)
- if GnRH agonist completely relieves symptoms, may consider definitive surgery (i.e. total abdominal hysterectomy + bilateral salpingo-oophorectomy)

Bipolar Disorders

BIPOLAR I / BIPOLAR II DISORDER

Definition

- Bipolar I Disorder
 - disorder in which **at least one manic or mixed episode** has occurred
 - commonly accompanied by at least 1 MDE but not required for diagnosis
- Bipolar II Disorder
 - disorder in which there is at least 1 MDE and at least 1 hypomanic episode
 - **no past manic or mixed episode**

Epidemiology

- prevalence: 0.6-0.9%; M:F = 1:1
- age of onset: teens to 20's

Risk Factors

- slight increase in upper socioeconomic groups
- 60-65% of bipolar patients have family history of major mood disorders

Classification

- classification of bipolar disorder involves describing the current or most recent mood episode as either manic, hypomanic, mixed or depressed
- the current or most recent episode can be further classified as without psychotic features, with psychotic features, with catatonic features, with postpartum onset, with seasonal pattern, with rapid cycling (at least 4 episodes of a mood disturbance in the previous 12 months that meet criteria for a Major Depressive, Manic, Mixed, or Hypomanic Episode)

A Randomized Controlled Trial of Cognitive Therapy for Bipolar Disorder: Focus on Long-term Change

J Clin Psychiatry, 2006 Feb; 67(2):277-86

Study: Randomized, blinded clinical trial.

Patients: 52 patients with DSM-IV bipolar 1 or 2 disorder.

Intervention: Patients allocated to either a 6 month trial of cognitive therapy (CT) with emotive techniques or treatment as usual. Both groups received mood stabilizers.

Main Outcomes: Relapse rates, dysfunctional attitudes, psychosocial functioning, hopelessness, self-control, medication adherence. Patients were assessed by independent raters blinded to treatment group.

Results: At 6 months, CT patients experienced fewer depressive symptoms and fewer dysfunctional attitudes. There was a non-significant ($p=.06$) trend to greater time to depressive relapse. At 12 month follow up, CT patients had lower Young Mania Rating scores and improved behavioural self-control. At 18 months, CT patients reported less severity of illness.

Conclusions: CT appears to provide benefits in the 12 months succeeding completion of therapy.

Treatment

- biological: mood stabilizers, anticonvulsants, antipsychotics, antidepressants, ECT (**Note:** Treatment of bipolar depression must be done extremely cautiously, as a switch from depression to mania can result. Monotherapy with antidepressants should be avoided)
- psychological: supportive and psychodynamic psychotherapy, cognitive or behavioural therapy
- social: vocational rehabilitation, leave of absence from school/work, drug and EtOH cessation, substitute decision maker for finances, sleep hygiene, social skills training, education for family members

CYCLOTHYMIA

Diagnosis

- presence of numerous periods of hypomanic and depressive symptoms (not meeting criteria for MDE) for **≥ 2 years**; never without symptoms for **>2 months**
- no MDE, manic or mixed episodes; no evidence of psychosis
- symptoms are not due to the direct physiological effects of a substance or GMC
- symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

Treatment

- similar to Bipolar I
- anticonvulsants \pm psychotherapy



Anxiety Disorders

Definition

- anxiety is a universal human characteristic involving tension, apprehension, or even terror, which serves as an adaptive mechanism to warn about an external threat by activating the sympathetic nervous system (fight or flight)
- manifestations of anxiety can be described along a continuum of physiology, psychology, and behaviour
 - physiology – main brain structure involved is the amygdala; neurotransmitters involved include serotonin, cholecystokinin, epinephrine, norepinephrine, dopamine
 - psychology – one's perception of a given situation is distorted which causes one to believe it is threatening in some way
 - behaviour – once feeling threatened, one responds by escaping or facing the situation, thereby causing a disruption in daily functioning
- anxiety becomes pathological when
 - fear is greatly out of proportion to risk/severity of threat
 - response continues beyond existence of threat or becomes generalized to other similar or dissimilar situations
 - social or occupational functioning is impaired

Differential Diagnosis

Table 3. Differential Diagnosis of Anxiety Disorders

Cardiovascular	Post-MI, arrhythmia, congestive heart failure, pulmonary embolus, mitral valve prolapse
Respiratory	Asthma, COPD, pneumonia, hyperventilation
Endocrine	Hyperthyroidism, pheochromocytoma, hypoglycemia, hyperadrenalism, hyperparathyroidism
Metabolic	Vitamin B ₁₂ deficiency, porphyria
Neurologic	Neoplasm, vestibular dysfunction, encephalitis
Substance-Induced	Intoxication (caffeine, amphetamines, cocaine, thyroid preparations, OTC for colds/decongestants), withdrawal (benzodiazepines, alcohol)
Other Psychiatric Disorders	Psychotic disorders, mood disorders, personality disorders (OCPD), somatoform disorders

Medical Workup of Anxiety Disorder

- routine screening: physical examination, CBC, thyroid function test, electrolytes, urinalysis, urine drug screening
- additional screening: neurological consultation, chest x-ray, electrocardiogram (ECG), CT scan

Panic Disorder

DSM-IV-TR Diagnostic Criteria for Panic Disorder without Agoraphobia

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A. both (1) and (2)

- (1) recurrent unexpected panic attacks: a discrete period of intense fear or discomfort, in which **≥4** of the following symptoms develop abruptly and reach a **peak within 10 minutes**
 - ♦ palpitations, pounding heart, or accelerated heart rate
 - ♦ sweating
 - ♦ trembling or shaking
 - ♦ sensations of shortness of breath or smothering
 - ♦ feeling of choking
 - ♦ chest pain or discomfort
 - ♦ nausea or abdominal distress
 - ♦ feeling dizzy, unsteady, lightheaded, or faint
 - ♦ derealization (feelings of unreality) or depersonalization (being detached from oneself)
 - ♦ fear of losing control or going crazy
 - ♦ fear of dying
 - ♦ paresthesias (numbness or tingling sensations), chills or hot flushes
- (2) at least one of the attacks has been followed by **1 month** (or more) of **≥1** of the following
 - ♦ persistent concern about having additional attacks
 - ♦ worry about the implications of the attack or its consequences (e.g. losing control, having a heart attack, "going crazy")
 - ♦ a significant change in behavior related to the attacks

B. absence of agoraphobia

C. the panic attacks are not due to the direct physiological effects of a substance or GMC

D. the panic attacks are not better accounted for by another mental disorder, such as Social Phobia, Specific Phobia, Obsessive-Compulsive Disorder, Post-Traumatic Stress Disorder, Separation Anxiety Disorder

Epidemiology

- prevalence: 1.5-5% (one of the top five most common reasons to see a family doctor); M:F = 1:2-3
- onset: average late 20's, familial pattern

Treatment

- psychological
 - supportive psychotherapy, relaxation techniques (visualization, box-breathing), cognitive behavioural therapy (correct distorted thinking, desensitization/exposure therapy)
- biological
 - SSRIs: fluoxetine, citalopram, paroxetine, fluvoxamine, sertraline
 - SNRI: venlafaxine
 - with SSRI/SNRI start low, go slow, aim high to prevent non-compliance due to physical side effects, explain symptoms to expect prior to initiation
 - other antidepressants (TCAs: clomipramine, imipramine, mirtazapine, MAOIs)
 - ♦ consider avoiding bupropion due to stimulating effects
 - benzodiazepines (short term, low dose, regular schedule, long half-life, no prn)

Prognosis

- 6-10 years post-treatment: 30% well, 40-50% improved, 20-30% no change or worse
- clinical course: chronic, but episodic with psychosocial stressors

Panic Disorder with Agoraphobia

- agoraphobia
 - anxiety about being in places or situations from which escape might be difficult (or embarrassing) or where help may not be available in the event of having an unexpected panic attack
 - fears commonly involve situations: being out alone, being in a crowd, standing in a line, or travelling on a bus
- situations are avoided, endured with anxiety or panic, or require companion
- **treatment:** as per panic disorder

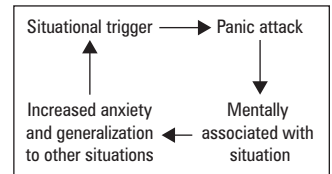


Figure 1. Panic Attack



Criteria for Panic Disorder (≥4)

STUDENTS FEAR the 3 C's

Sweating
Trembling
Unsteadiness, dizziness
Depersonalization, Derealization
Excessive heart rate, palpitations
Nausea
Tingling
Shortness of breath

Fear of dying, losing control, going crazy

3 C's: Chest pain, Chills, Choking

Generalized Anxiety Disorder (GAD)

DSM-IV-TR Diagnostic Criteria for Generalized Anxiety Disorder

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- A. excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least **6 months**, about a number of events or activities (such as work or school performance)
- B. the person finds it difficult to control the worry

**Criteria for GAD (≥ 3)****BE SKIM**

Blank mind
Easily fatigued
Sleep disturbance
Keyed up
Irritability
Muscle tension

- C. the anxiety and worry are associated with ≥ 3 of the following 6 symptoms (with at least some symptoms present for more days than not for the past **6 months**)
Note: Only one item is required in children
1. restlessness or feeling keyed up or on edge
 2. being easily fatigued
 3. difficulty concentrating or mind going blank
 4. irritability
 5. muscle tension
 6. sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
- D. the focus of the anxiety and worry is not confined to features of an Axis I disorder, such as panic disorder, social phobia, etc.
- E. the anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- F. the disturbance is not due to the direct physiological effects of a substance or a GMC and does not occur exclusively during a Mood Disorder, a Psychotic Disorder, or a Pervasive Developmental Disorder

Epidemiology

- 1-year prevalence: 3-8%; M:F = 1:2
 - if considering only those receiving inpatient treatment, ratio is 1:1
- most commonly presents in early adulthood

Treatment

- lifestyle: caffeine and EtOH avoidance, sleep hygiene
- psychological: psychotherapy, relaxation, mindfulness, and CBT
- biological
 - benzodiazepines (short term, low dose, regular schedule, long half-life, no prn)
 - buspirone (tid dosing)
 - others: SSRIs/SNRI, TCAs, beta-blockers
 - avoid bupropion due to stimulating effects
- combinations of above

Prognosis

- chronically anxious adults become less so with age
- depends on pre-morbid personality functioning, stability of relationships, work, and severity of environmental stress
- difficult to treat

Phobic Disorders

Specific Phobia

- definition: marked and persistent fear that is excessive or unreasonable, cued by presence or anticipation of a specific object or situation
- lifetime prevalence 12-16%; M:F ratio variable
- types: animal/insect, environment (heights, storms), blood/injection/injury, situational (airplane, closed spaces), other (loud noise, clowns)

Social Phobia (Social Anxiety Disorder)

- definition: marked and persistent fear of social or performance situations in which person is exposed to unfamiliar people or to possible scrutiny by others; person fears he/she will act in a way that may be humiliating or embarrassing (e.g. public speaking, initiating or maintaining conversation, dating, eating in public)
- lifetime prevalence may be as high as 13-16%; M<F

Diagnostic Criteria for Phobic Disorders

- exposure to stimulus almost invariably provokes an immediate anxiety response; may present as a panic attack
- person recognizes fear as excessive or unreasonable
- situations are avoided or endured with anxiety/distress
- significant interference with daily routine, occupational/social functioning, and/or marked distress
- if person is <18 years, duration is at least 6 months

Treatment

- psychological
 - exposure therapy/desensitization, insight-oriented psychotherapy
 - behavioural therapy is more efficacious than medication
- biological
 - beta-blockers or benzodiazepines in acute situations (e.g. public speaking)
 - SSRIs, MAOIs; clomipramine

Prognosis

- chronic

Obsessive-Compulsive Disorder (OCD)

DSM-IV-TR Diagnostic Criteria for Obsessive Compulsive Disorder

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A. either obsessions or compulsions

obsessions as defined by (1), (2), (3), and (4)

- (1) recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress
- (2) the thoughts, impulses, or images are not simply excessive worries about real-life problems
- (3) the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action
- (4) the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion)

compulsions as defined by (1) and (2)

- (1) repetitive behaviours or mental acts that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly
- (2) the behaviours or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviours or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive

B. at some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable (ego-dystonic)

Note: This does not apply to children

C. the obsessions or compulsions cause marked distress, are time consuming (take ≥ 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships

D. if another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g. preoccupation with food in the presence of an Eating Disorder)

E. the disturbance is not due to the direct physiological effects of a substance or a GMC

Epidemiology

- lifetime prevalence rates 2-3%; M=F
- rate of OCD in first-degree relatives is higher than in the general population

Treatment

- CBT: desensitization, flooding, thought stopping, implosion therapy, aversive conditioning
- pharmacotherapy
 - clomipramine, SSRIs (higher doses and longer treatment needed than for treatment of depression, i.e. up to 8-12 weeks)
 - atypical and typical antipsychotics – risperidone, haloperidol

Prognosis

- tends to be refractory and chronic

Post-Traumatic Stress Disorder (PTSD)

DSM-IV-TR Diagnostic Criteria for Post-Traumatic Stress Disorder

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A. the person has been **exposed to a traumatic event** in which both of the following were present

- (1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
- (2) the person's response involved intense fear, helplessness, or horror.

Note: In children, this may be expressed instead by disorganized or agitated behaviour

B. the **traumatic event is persistently re-experienced** in one (or more) of the following ways:

- (1) recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions

Note: In young children, repetitive play may occur in which themes or aspects of the trauma are expressed

- (2) recurrent distressing dreams of the event

Note: In children, there may be frightening dreams without recognizable content

- (3) acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated)

Note: In young children, trauma-specific reenactment may occur

- (4) intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

- (5) physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event



Criteria for Post-Traumatic Stress Disorder

TRAUMA

Traumatic event

Re-experience the event

Avoidance of stimuli associated with the trauma

Unable to function

More than a Month

Arousal increased

- C. persistent **avoidance of stimuli** associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by ≥ 3 of the following:
 - (1) efforts to avoid thoughts, feelings, or conversations associated with the trauma
 - (2) efforts to avoid activities, places, or people that arouse recollections of the trauma
 - (3) inability to recall an important aspect of the trauma
 - (4) markedly diminished interest or participation in significant activities
 - (5) feeling of detachment or estrangement from others
 - (6) restricted range of affect (e.g. unable to have loving feelings)
 - (7) sense of a foreshortened future (e.g. does not expect to have a career, marriage, children, or a normal life span)
- D. persistent **symptoms of increased arousal** (not present before the trauma), as indicated by ≥ 2 of the following:
 - (1) difficulty falling or staying asleep
 - (2) irritability or outbursts of anger
 - (3) difficulty concentrating
 - (4) hypervigilance
 - (5) exaggerated startle response
- E. duration of the disturbance (symptoms in Criteria B, C, and D) is ≥ 1 month
- F. the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

Epidemiology

- prevalence in general population: 7%
- men's trauma is most commonly combat experience; women's trauma is usually physical or sexual assault

Treatment

- CBT: systematic desensitization, relaxation techniques, thought stopping
- biological
 - SSRIs
 - benzodiazepines (for acute anxiety)
 - first-line adjunct – atypical antipsychotics (quetiapine, olanzapine, risperidone)
- Eye Movement Desensitization and Reprocessing (EMDR): an experimental method of reprocessing memories of distressing events by recounting them while using a form of dual attention stimulation such as eye movements, bilateral sound, or bilateral tactile stimulation

Complications

- substance abuse, relationship difficulties, depression, impaired social and occupational functioning, Axis II disorders



Adjustment Disorder

DSM-IV-TR Diagnostic Criteria for Adjustment Disorder

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- A. the development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring **within 3 months** of the onset of the stressor(s)
- B. these symptoms or behaviours are clinically significant as evidenced by either of the following
 - (1) marked distress that is in excess of what would be expected from exposure to the stressor
 - (2) significant impairment in social or occupational (academic) functioning
- C. the stress-related disturbance does not meet the criteria for another specific Axis I disorder and is not merely an exacerbation of a pre-existing Axis I or Axis II disorder
- D. the symptoms do not represent bereavement
- E. once the stressor (or its consequences) has terminated, the symptoms do not persist for more than an additional 6 months
 - specify if
 - ♦ **acute**: if the disturbance lasts less than 6 months
 - ♦ **chronic**: if the disturbance lasts for 6 months or longer
 - adjustment disorders are coded based on the subtype, which is selected according to the predominant symptoms

Classification

- types of stressors
 - single (e.g. termination of romantic relationship)
 - multiple (e.g. marked business difficulties and marital problems)
 - recurrent (e.g. seasonal business crises)
 - continuous (e.g. living in a crime-ridden neighbourhood)
 - developmental events (e.g. going to school, leaving parental home, getting married, becoming a parent, failing to attain occupational goals, retirement)
 - **Note**: the specific stressor is specified on Axis IV

- **subtypes**, adjustment disorder with:
 - depressed mood
 - anxiety
 - mixed anxiety and depressed mood
 - disturbance of conduct
 - mixed disturbance of emotions and conduct
 - unspecified

Epidemiology

- M=F

Treatment

- brief psychotherapy (group, individual), crisis intervention
- biological
 - benzodiazepines may be used for those with anxiety symptoms (short-term, low-dose, regular schedule, long half-life, no prn)
 - SSRIs for both depressed and anxiety symptoms

Cognitive Disorders



Delirium

- see Neurology, N10

DSM-IV-TR Diagnostic Criteria for Delirium due to a GMC

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- disturbance of consciousness** (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention
- a **change in cognition** (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia
- the disturbance develops over a short period of time (usually **hours to days**) and tends to fluctuate during the course of the day
- there is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a GMC

Clinical Presentation and Assessment

- common symptoms
 - wandering attention
 - distractibility
 - disorientation (time, place, rarely person)
 - misinterpretations, illusions, hallucinations
 - speech/language disturbances (dysarthria, dysnomia, dysgraphia)
 - affective symptoms (anxiety, fear, depression, irritability, anger, euphoria, apathy)
 - shifts in psychomotor activity (groping/picking at clothes, attempts to get out of bed when unsafe, sudden movements, sluggishness, lethargy)
- Folstein Mini Mental Status exam is helpful to assess baseline of altered mental state – i.e. score will improve as symptoms resolve

Risk Factors

- hospitalization (incidence 10-40%)
- nursing home residents (incidence 60%)
- childhood (e.g. febrile illness, anticholinergic use)
- old age (especially males)
- severe illness (e.g. cancer, AIDS)
- pre-existing cognitive impairment or brain pathology
- recent anesthesia
- substance abuse

**Delirium****I WATCH DEATH**

Infectious

Withdrawal from drugs

Acute metabolic disorder

Trauma

CNS pathology

Hypoxia

Deficiencies in vitamins

Endocrinopathies

Acute vascular insults

Toxins

Heavy metals

Etiology

- Infectious (encephalitis, meningitis, UTI, pneumonia)
- Withdrawal (alcohol, barbiturates, benzodiazepines)
- Acute metabolic disorder (electrolyte imbalance, hepatic or renal failure)
- Trauma (head injury, postoperative)
- CNS pathology (stroke, hemorrhage, tumour, seizure disorder, Parkinson's)
- Hypoxia (anemia, cardiac failure, pulmonary embolus)
- Deficiencies (vitamin B₁₂, folic acid, thiamine)
- Endocrinopathies (thyroid, glucose, parathyroid, adrenal)
- Acute vascular (shock, vasculitis, hypertensive encephalopathy)
- Toxins: substance use, alcohol or alcohol withdrawal, sedatives or sedative withdrawal, narcotics (especially morphine), anesthetics, anticholinergics, anticonvulsants, dopaminergic agents, steroids, insulin, glyburide, antibiotics (especially quinolones), NSAIDs
- Heavy metals (arsenic, lead, mercury)

Investigations

- standard: CBC and differential, electrolytes, calcium, phosphate, magnesium, glucose, ESR, LFTs, Cr, BUN, TSH, vitamin B₁₂, folate, albumin, urine C&S, R&M
- as indicated: ECG, CXR, CT head, toxicology/heavy metal screen, VDRL, HIV, LP, EEG (typically abnormal: generalized slowing or fast activity), blood cultures
- indications for radiological investigations: focal neurological deficit, acute change in status, anticoagulant use, acute incontinence, gait abnormality, history of cancer

Management

- intrinsic
 - identify and treat underlying cause immediately
 - stop all non-essential medications
 - maintain nutrition, hydration, electrolyte balance and monitor vitals
- extrinsic
 - environment should be quiet and well-lit
 - optimize hearing and vision
 - room near nursing station for closer observation; constant care if patient jumping out of bed, pulling out lines
 - family member present for reassurance and re-orientation
 - calendar, clock for orientation cues
- biological
 - haloperidol or risperidone (low dose)
 - lorazepam
- physical restraints if patient becomes violent

Prognosis

- up to 50% 1 year mortality rate after episode of delirium

Dementia

- see Neurology, N11

DSM-IV-TR Diagnostic Criteria for Dementia (Alzheimer's Type)

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- A. the development of multiple cognitive deficits manifested by both
 1. **memory impairment** (impaired ability to learn new information or to recall previously learned information)
 2. **≥1 of the following cognitive disturbances:**
 - ◆ aphasia (language disturbance)
 - ◆ apraxia (impaired ability to carry out motor activities despite intact motor function)
 - ◆ agnosia (failure to recognize or identify objects despite intact sensory function)
 - ◆ disturbance in executive functioning (i.e. planning, organizing, sequencing, abstracting)
- B. the cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning
- C. the course is characterized by gradual onset and continuing cognitive decline
- D. the cognitive deficits in Criteria A1 and A2 are not due to any of the following:
 1. other central nervous system conditions that cause progressive deficits in memory and cognition
 2. systemic conditions that are known to cause dementia
 3. substance-induced conditions
- E. the deficits do not occur exclusively during the course of a delirium
- F. the disturbance is not better accounted for by another Axis I disorder

**Most Common Types of Dementia**

Alzheimer's dementia

Vascular dementia

Lewy-Body dementia

Fronto-temporal dementia

Epidemiology

- prevalence increases with age: 10% in patients over 65 years of age; 25% in patients over 85 years of age
- prevalence is increased in people with Down syndrome and head trauma
- Alzheimer's dementia comprises >50% of cases; vascular causes comprise approximately 15% of cases (other causes of dementia – see [Neurology](#), N12)
- 10% of dementia cases are potentially curable (mainly vascular etiology)
- average duration of illness from onset of symptoms to death is 8-10 years

Subtypes

- with or without behavioural disturbance (e.g. wandering, agitation)
- early onset: age of onset <65 years
- late onset: age of onset >65 years

Investigations (rule out reversible causes)

- standard: see *Delirium*, PS18
- as indicated: VDRL, HIV, SPECT, CT head in dementia
- indications for CT head, (see *Delirium* section) plus: age <60, rapid onset (unexplained decline in cognition or function over 1-2 months), dementia of relatively short duration (<2 years), recent significant head trauma, unexplained neurological symptoms (new onset of severe headache/seizures)

Management

- treat medical problems and prevent others
- provide orientation cues (e.g. clock, calendar)
- provide education and support for patient and family (day programs, respite care, support groups, home care)
- consider long-term care plan (nursing home) and power of attorney/living will
- inform Ministry of Transportation about patient's inability to drive safely
- consider pharmacological therapy
 - cholinesterase inhibitors [e.g. donepezil (Aricept®)] for mild to severe disease
 - glutamatergic NMDA receptor antagonist (e.g. memantine) for moderate to severe disease
 - low-dose neuroleptics (haloperidol, risperidone) and antidepressants if behavioural or emotional symptoms prominent – start low and go slow
 - reassess pharmacological therapy every 3 months

Risk of Death with Atypical Antipsychotic Drug Treatment for Dementia

JAMA 2005; 294(15):1934-1943

Purpose: To assess the evidence for increased mortality from atypical antipsychotic drug treatment for delusions, aggression and agitation in dementia.

Study Characteristics: Meta-analysis of 15 RCTs with 5110 patients.

Participants: Patients with Alzheimer disease or dementia.

Results: Death occurred more often among patients randomized to drugs (118 [3.5%] vs. 40 [2.3%]). The odds ratio by meta-analysis was 1.54; 95% confidence interval (CI), 1.06-2.23; P=0.02). Sensitivity analyses did not show evidence for differential risks for individual drugs or diagnosis.

Conclusions: Atypical antipsychotic drugs may be associated with a small increased risk of death compared to placebo. This risk should be considered within the context of medical need for the drugs, efficacy evidence, medical comorbidity, and the efficacy and safety of alternatives.

Table 4. Comparison of Dementia, Delirium and Pseudodementia of Depression

	Dementia	Delirium	Pseudodementia of Depression
Onset	Gradual/step-wise decline	Acute (hours – days)	Subacute
Duration	Months – years	Days – weeks	Variable
Natural History	Progressive Usually irreversible	Fluctuating, reversible High morbidity/mortality in very old	Recurrent Usually reversible
Level of Consciousness	Normal	Fluctuating (over 24 hours)	Normal
Attention	Not initially affected	Decreased (wandering, easy distraction)	Difficulty concentrating
Orientation	Intact initially	Impaired (usually to time and place), fluctuates	Intact
Behaviour	Disinhibition, impairment in ADL/IADL, personality change, loss of social graces	Severe agitation/retardation	Importuning, self-harm/suicide
Psychomotor	Normal	Fluctuates between extremes	Slowing
Sleep Wake Cycle	Fragmented sleep at night	Reversed sleep wake cycle	Early morning awakening
Mood and Affect	Labile but not usually anxious	Anxious, irritable, fluctuating	Depressed, stable
Cognition	Decreased executive functioning, paucity of thought	Fluctuating preceded by mood changes	Fluctuating
Memory Loss	Recent, eventually remote	Marked recent	Recent
Language	Agnosia, aphasia, decreased comprehension, repetition, speech (echolalia, palilalia)	Dysnomia, dysgraphia, speech rambling, irrelevant, incoherent, subject changes	Not affected
Delusions	Compensatory	Nightmarish and poorly formed	Nihilistic, somatic
Hallucinations	Variable	Visual common	Less common, auditory predominates
Quality of Hallucinations	Vacuous/bland	Frightening/bizarre	Self-deprecatory
Medical Status	Variable	Acute illness, drug toxicity	R/O systemic illness, meds



Substance-Related Disorders

Types of Substance Disorders

- 47% of those with substance abuse have mental health problems
- 29% of those with a mental health disorder have a substance use disorder
- 47% of those with schizophrenia, 25% of those with an anxiety disorder

A. Substance-use disorders

1. **substance abuse:** maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by ≥ 1 of the following occurring within a 12 month period
 - ♦ recurrent use resulting in failure to fulfill major role obligation
 - ♦ recurrent use in situations in which it is physically hazardous (e.g. driving)
 - ♦ recurrent substance-related legal problems
 - ♦ continued use despite interference with social or interpersonal function
2. **substance dependence:** maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by ≥ 3 occurring at any time in the same 12 month period
 - ♦ tolerance (need for increased amount to achieve intoxication or diminished effect with same amount of substance)
 - ♦ withdrawal/use to avoid withdrawal
 - ♦ taken in larger amount or over longer period than intended
 - ♦ persistent desire or unsuccessful efforts to cut down
 - ♦ excessive time to procure, use substance, or recover from its effects
 - ♦ important interests/activities given up or reduced
 - ♦ continued use despite physical/psychological problem caused/exacerbated by substance

B. Substance-induced disorders

1. **substance intoxication:** reversible physiological and behavioural changes due to recent exposure to psychoactive substance
2. **substance withdrawal:** substance-specific syndrome that develops following cessation of or reduction in dosage of regularly used substances



Substance Dependence

The 3 Cs

Compulsive use
Loss of Control
Consequences of use

Alcohol

- see Family Medicine, FM10 and Emergency Medicine, ER48

History

- validated screening questionnaire
 - C ever felt the need to Cut down on drinking?
 - A ever felt Annoyed at criticism of your drinking?
 - G ever feel Guilty about your drinking?
 - E ever need a drink first thing in morning (Eye opener)?
 - for men, a score of ≥ 2 is a positive screen; for women, a score of ≥ 1 is a positive screen
 - if positive CAGE, then assess further to distinguish between problem drinking and alcohol dependence

General Assessment

- When was your last drink?
- Do you have to drink more to get the same effect?
- Do you get shaky or nauseous when you stop drinking?
- Have you ever had a withdrawal seizure?
- How much time and effort do you put into obtaining alcohol?
- Has your drinking affected your ability to work, go to school, or have relationships?
- Have you suffered any legal consequences?
- Has your drinking caused any medical problems?

Table 5. Differentiating Moderate Drinking from a Drinking Problem

Moderate Drinking	Drinking Problem
Drinking within the recommended guidelines (U.S. Department of Health and Human Services) Men: 2 or less/day (≤ 14 /wk) Women: 1 or less/day (≤ 9 /wk) Elderly: 1 or less/day	Drinking above the recommended guidelines, associated with: <ul style="list-style-type: none"> • Drinking to reduce depression or anxiety • Loss of interest in food • Lying/hiding drinking habits • Drinking alone • Injuring self or others while intoxicated • Was drunk more than three or four times over the last year • Increasing tolerance • Withdrawal symptoms: feeling irritable, resentful, unreasonable when not drinking • Experiencing medical, social, or financial problems caused by drinking



A "Standard Drink"

Spirit (40%) – 1.5 oz. or 43 mL
Table Wine (12%) – 5 oz. or 142 mL
Fortified Wine (18%) – 3 oz. or 85 mL
Regular Beer (5%) – 12 oz. or 341 mL

OR

1 pint beer = 1.5 SD
1 bottle wine = 5 SD
1 "mickey" = 8 SD
"26-er" = 17 SD
"40 oz." = 27 SD



Make sure to ask about other alcohols: mouthwash, rubbing alcohol, methanol, ethylene glycol, aftershave (may be used as a cheaper alternative)



Alcohol abuse can only be diagnosed in the absence of alcohol dependence. The criteria for abuse and dependence are outlined under substance-use disorders.

Alcohol Intoxication

- legal limit for impaired driving is 10.6 mmol/L (50 mg/dL) reached by 2-3 drinks/h for men and 1-2 drinks/h for women
- coma can occur with 60+ mmol/L (non-tolerant drinkers) and 90-120 mmol/L (tolerant drinkers)

Alcohol Withdrawal

- occurs within 12 to 48 hours after prolonged heavy drinking and can be life-threatening
- alcohol withdrawal can be described as having 4 stages, however not all stages may be experienced
 - stage 1 (onset 6-12 hours after last drink): tremor, sweating, agitation, anorexia, cramps, diarrhea, sleep disturbance
 - stage 2 (onset 1-7 days): visual, auditory, olfactory or tactile hallucinations
 - stage 3 (onset 12-72 hours and up to 7 days): seizures, usually tonic-clonic nonfocal and brief
 - stage 4 (onset 3-5 days): delirium tremens, confusion, delusions, hallucinations, agitation, tremors, autonomic hyperactivity (fever, tachycardia, hypertension)
- course: in young almost completely reversible; elderly often left with cognitive deficits
- mortality rate 20% if untreated

**Delirium Tremens****(alcohol withdrawal delirium)**

Autonomic hyperactivity (diaphoresis, tachycardia, increased respiration)

Hand tremor

Insomnia

Psychomotor agitation

Anxiety

Nausea or vomiting

Tonic-clonic seizures

Visual/tactile/auditory hallucinations

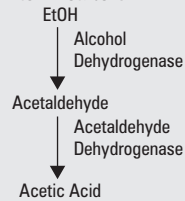
Persecutory delusions

Management of Alcohol Withdrawal

- monitor using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) scoring system
 - areas of assessment include
 - ♦ nausea and vomiting
 - ♦ tactile disturbances
 - ♦ tremor
 - ♦ auditory disturbances
 - ♦ agitation
 - ♦ paroxysmal sweats
 - ♦ visual disturbances
 - ♦ anxiety
 - ♦ headache, fullness in head
 - ♦ orientation and clouding of sensorium
 - all categories are scored from 0-7 (except: orientation/sensorium 0-4), maximum score of 67
 - ♦ mild <10
 - ♦ moderate 10-20
 - ♦ severe >20
- basic treatment protocol using CIWA-A scale
 - diazepam 20 mg PO q1-2h prn until CIWA-A <10 points; tapering dose not required
 - observe 1-2 h after last dose and re-assess on CIWA-A scale
 - thiamine 100 mg IM then 100 mg PO OD for 3 days
 - supportive care (hydration and nutrition)
- if history of withdrawal seizures
 - diazepam 20 mg PO q1h for minimum of three doses regardless of subsequent CIWA scores
- if history of seizure disorder or multiple withdrawal seizures despite diazepam, use anti-seizure medication (e.g. Dilantin)
- if oral diazepam not tolerated
 - diazepam 2-5 mg IV/min – maximum 10-20 mg q1h; or lorazepam SL
- if >65 years old or severe liver disease, severe asthma, or respiratory failure, use short acting benzodiazepine
 - lorazepam PO/SL/IM 1-4 mg q1-2h
- if hallucinations are present
 - haloperidol 2-5 mg IM/PO q1-4h – max 5 doses/day or atypical antipsychotics (olanzapine, risperidone)
 - diazepam 20 mg x 3 doses as seizure prophylaxis (haloperidol lowers seizure threshold)
- admit to hospital if
 - still in withdrawal after >80 mg of diazepam
 - delirium tremens, recurrent arrhythmias, or multiple seizures
 - medically ill or unsafe to discharge home

Wernicke-Korsakoff Syndrome

- alcohol-induced amnesic disorders due to thiamine deficiency
- necrotic lesions – mammillary bodies, thalamus, brainstem
- Wernicke's encephalopathy (acute and reversible): triad of nystagmus (CN VI palsy), ataxia and confusion
- Korsakoff's syndrome (chronic and only 20% reversible with treatment): anterograde amnesia and confabulations; cannot occur during an acute delirium or dementia and must persist beyond usual duration of intoxication/withdrawal
- management
 - Wernicke's: thiamine 100 mg PO OD x 1-2 weeks
 - Korsakoff's: thiamine 100 mg PO bid/tid x 3-12 months

**EtOH Metabolism****Opioid Antagonists:
Naltrexone vs. Naloxone****Naltrexone (Revia®)**

- Used for opioid and EtOH dependence
- Long half life (hours)

Naloxone (Narcan®):

- Used for life-threatening CNS/respiratory depression in opioid overdose
- Short half life (<1 h)
- Very fast acting (mins)
- High affinity for opioid receptor
- Induces opioid withdrawal symptoms

**Common Presentations of Drug Use**

System	Findings
General	Weight loss (especially cocaine, heroin) Injected conjunctiva (cannabis) Pinpoint pupils (opioids) Track marks (injection drugs)
MSK	Trauma
GI	Viral hepatitis (injection drugs) Unexplained elevations in ALT (injection drugs)
Behavioural	Missed appointments Non-compliance Drug-seeking (especially benzodiazepines, opioids)
Psychological	Insomnia Fatigue Depression Flat affect (benzodiazepines, barbiturates) Paranoia (cocaine) Psychosis (cocaine, cannabis, hallucinogens)
Social	Marital discord Family violence Work/school absenteeism and poor performance

Treatment of Alcohol Dependence**Non-pharmacological**

- behaviour modification: hypnosis, relaxation training, aversion therapy, assertiveness training, operant conditioning
- supportive services: half-way houses, detoxification centres, Alcoholics Anonymous
- psychotherapy, motivational interviewing
- medications important as adjunctive treatment: SSRIs, ondansetron, topiramate

Pharmacological

- naltrexone: opioid antagonist, shown to be successful in reducing the “high” associated with alcohol, moderately effective in reducing cravings, frequency or intensity of alcohol binges
- disulfiram (Antabuse®): blocks oxidation of alcohol (blocks acetaldehyde dehydrogenase); with alcohol consumption, acetaldehyde accumulates to cause a toxic reaction (vomiting, tachycardia, death); if patient relapses, must wait 48 hours before restarting Antabuse®

Opioids

- types of opioids: heroin, morphine, oxycodone, Tylenol #3® (codeine)
- major risks associated with the use of contaminated needles; increased risk of hepatitis B and C, bacterial endocarditis, HIV

Acute Intoxication

- direct effect on receptors in CNS resulting in decreased pain perception, sedation, decreased sex drive, nausea/vomiting, decreased GI motility (constipation and anorexia), and respiratory depression

Toxic Reaction

- typical syndrome includes shallow respirations, miosis, bradycardia, hypothermia, decreased level of consciousness
- treatment
 - ABC's
 - IV glucose
 - naloxone hydrochloride (Narcan®): 0.4 mg up to 2 mg IV for diagnosis
 - treatment: intubation and mechanical ventilation, ± naloxone drip, until patient alert without naloxone (up to 48+ hours with long-acting opioids)
- caution with longer half-life; may need to observe for toxic reaction for at least 24 hours

Withdrawal

- symptoms: depression, insomnia, drug-craving, myalgias, nausea, chills, autonomic instability (lacrimation, rhinorrhea, piloerection)
- onset: 6-12 h, duration: 5-10 days
- complications: loss of tolerance (overdose on relapse), miscarriage, premature labour
- management: long-acting oral opioids (methadone, buprenorphine), alpha-adrenergic agents (clonidine)

Treatment of Chronic Abuse

- psychosocial treatment (e.g. Narcotics Anonymous); usually emphasize total abstinence
- long-term treatment may include withdrawal maintenance treatment
 - methadone relieves drug cravings and withdrawal symptoms without inducing sedation or euphoria
- naltrexone or naloxone (opioid antagonists) may also be used to extinguish drug-seeking behaviour

Cocaine

- street names: blow, C, coke, crack, flake, freebase, rock, snow
- alkaloid extracted from leaves of the coca plant; blocks presynaptic uptake of dopamine (causing euphoria), norepinephrine and epinephrine (causing vasospasm, hypertension)
- self-administered by inhalation or intravenous route

Intoxication

- elation, euphoria, pressured speech, restlessness, sympathetic stimulation (e.g. tachycardia, mydriasis, sweating)
- prolonged use may result in paranoia and psychosis

Overdose

- medical emergency: hypertension, tachycardia, tonic-clonic seizures, dyspnea, and ventricular arrhythmias
- treatment with IV diazepam to control seizures and propranolol or labetalol to manage hypertension and arrhythmias

Withdrawal

- initial “crash” (1-48 hours): increased sleep, increased appetite
- withdrawal (1-10 weeks): dysphoric mood plus fatigue, irritability, vivid, unpleasant dreams, insomnia or hypersomnia, psychomotor agitation or retardation
- complications: relapse, suicide (significant increase in suicide during withdrawal period)
- management: supportive management

Treatment of Chronic Abuse

- optimal treatment not established
- psychotherapy, group therapy, and behaviour modification useful in maintaining abstinence
- studies of dopamine agonists to block cravings show inconsistent results

Complications

- cardiovascular: arrhythmias, MI, CVA, ruptured AAA
- neurologic: seizures
- psychiatric: psychosis, paranoia, delirium, suicidal ideation

Cannabis

- marijuana, hashish (hash) and hash oil come from cannabis sativa
- street names: weed, herb, chronic, jay, bud, blunt, bomb, doobie, hydro, sinsemilla, hash, joint, pot, grass, reefer, Mary Jane (MJ), ganja, homegrown, dope, spliff
- marijuana is the most often used illicit drug
- psychoactive substance: delta-9-tetrahydrocannabinol (Δ^9 -THC)
- smoking is the most common mode of self-administration
- intoxication characterized by tachycardia, conjunctival vascular engorgement, dry mouth, increased appetite, increased sense of well-being, euphoria/laughter, muscle relaxation, impaired performance on psychomotor tasks including driving
- high doses can cause depersonalization, paranoia, and anxiety
- may trigger psychosis and schizophrenia in predisposed individuals
- chronic use associated with tolerance and an apathetic, amotivational state
- cessation does not produce significant withdrawal phenomenon
- treatment of dependence includes behavioural and psychological interventions to maintain an abstinent state

Amphetamines

- types of amphetamines: amphetamine, methamphetamine, dextroamphetamine
- street names: speed, bennies, glass, crystal, crank, pep pills and uppers
- class of drugs structurally related to catecholamine neurotransmitters, includes methamphetamine (see *Club Drugs*, PS24)
- intoxication characterized by euphoria, improved concentration, sympathetic and behavioural hyperactivity
- at high doses can cause coma
- chronic use can produce a paranoid psychosis diagnostically similar to schizophrenia with agitation, paranoia, delusions and hallucinations
- withdrawal symptoms include dysphoria, fatigue, and restlessness
- antipsychotics useful in treatment of stimulant psychosis

Hallucinogens

- types of hallucinogens: LSD, mescaline, psilocybin, PCP, cannabis, ecstasy, salvia (see *Club Drugs*, PS24)
- LSD is a highly potent drug; intoxication characterized by tachycardia, hypertension, mydriasis, tremor, hyperpyrexia, and a variety of perceptual and mood changes
- high doses can cause depersonalization, paranoia, and anxiety
- no specific withdrawal syndrome characterized
- treatment of agitation and psychosis: support, reassurance, diminished stimulation; benzodiazepines or high potency antipsychotics seldom required

**Medical Uses of Marijuana**

- Anorexia-cachexia (AIDS, cancer)
- Spasticity, muscle spasms (multiple sclerosis, spinal cord injury)
- Levodopa-induced dyskinesia (Parkinson's Disease)
- Controlling tics and obsessive-compulsive behaviour (Tourette's syndrome)
- Reducing intra-ocular pressure (glaucoma)

Cannabis Use and Risk of Psychotic or Affective Mental Health Outcomes: A Systematic Review
The Lancet 2007; 370:319-328

Purpose: To review the evidence for cannabis use and occurrence of psychotic or affective mental health outcomes.

Study Characteristics: A meta-analysis of 35 population-based longitudinal studies, or case-control studies nested within longitudinal designs.

Results: There was an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted odds ratio = 1.41, 95% CI 1.20-1.65). Findings were consistent with a dose-response effect, with greater risk in people who used cannabis more frequently (2.09, 95% CI, 1.54-2.84). Findings for depression, suicidal thoughts and anxiety outcomes were less consistent. In both cases (psychotic and affective outcomes) a substantial confounding effect was present.

Conclusions: The findings are consistent with the view that cannabis increases risk of psychotic outcomes independent of transient intoxication effects, although evidence is less strong for affective outcomes. Although cannabis use and the development of psychosis are strongly associated, it is difficult to determine causality and it is possible that the association results from confounding factors or bias. The authors did conclude that there is sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life.

"Club Drugs"

Table 6. The Mechanism and Effects of Common "Club Drugs"

Drug	Mechanism	Effect	Adverse Effects	Dangerous Effects	Formulation/Route
MDMA ("Ecstasy", "X", "E")	Acts on serotonergic and dopaminergic pathways, properties of a hallucinogen and an amphetamine	Enhanced sensorium; feelings of well-being, empathy	Sweating, tachycardia, fatigue, muscle spasms (especially jaw clenching), ataxia	Hyperthermia, arrhythmias, DIC, rhabdomyolysis, renal failure, seizures, death, long-term neurotoxicity to serotonergic system (in animal models)	Tablet
Gamma Hydroxybutyrate (GHB, "G", "Liquid Ecstasy")	Biphasic dopamine response (inhibition then release) and releases opiate-like substance	Euphoric effects, increased aggression, impaired judgement	Sweating, tachycardia, fatigue, muscle spasms (especially jaw clenching), ataxia	Severe withdrawal from abrupt cessation of high doses: tremor, seizures, psychosis	Salt dissolved in water
Flunitrazepam (Rohypnol, "Roofies", "Rope", "The Forget Pill")	Potent benzodiazepine, rapid oral absorption	Sedation, psychomotor impairment, amnesic effects, decreased sexual inhibition	CNS depression with EtOH		Salt or powder Dissolved in water Tastes salty
Ketamine ("Special K", "Kit-Kat")	NMDA receptor antagonist, rapid-acting general anesthetic used in pediatrics	"Dissociative" state, profound amnesia/analgesia; hallucinations and sympathomimetic effects	Psychological distress, accidents due to intensity of experience and lack of bodily control	In overdose, decreased LOC, respiratory depression, catatonia	Tablet taken orally, crushed and dissolved or snorted
Methamphetamine ("speed", "meth", "chalk", "ice", "crystal")	Amphetamine stimulant, induces norepinephrine, dopamine and serotonin release	Rush begins in minutes, effects last 6-8 hours, increased activity, decreased appetite, general sense of well-being, tolerance occurs quickly, users often binge and crash	Short term use: high agitation, rage, violent behaviour, occasionally hyperthermia and convulsions	Long term use: addiction, anxiety, confusion, insomnia, paranoia, auditory and tactile hallucinations (esp. formication), delusions, mood disturbance, suicidal and homicidal thoughts, stroke, may be contaminated with lead, and IV users may present with acute lead poisoning	Smoked, snorted, injected, orally ingested, per rectum, per vagina
Phencyclidine ("PCP", "angel dust")	Not understood, used by vets to immobilize large animals	Amnesic, euphoric, hallucinatory state	Horizontal/vertical nystagmus, myoclonus, ataxia, and autonomic instability common (treat with diazepam IV)	Prolonged agitated psychosis (treat with haloperidol); high risk for suicide; violence towards others High dose can cause coma	Orally, smoked, or IV



Date Rape Drugs

GHB
Flunitrazepam (Rohypnol)
Ketamine



Formication – tactile hallucination that insects or snakes are crawling over or under the skin. Especially associated with crystal meth use.



Suicide

Epidemiology

- attempted:completed = 20:1
- M:F = 3:1 for completed; 1:4 for attempts

Risk Factors

- epidemiologic factors
 - age: increases after age 14; second most common cause of death for ages 15-24; highest rates in persons >65 years
 - sex: male
 - race/ethnic background: white or native Canadians on reserves
 - marital status: widowed/divorced
 - living situation: alone; no children <18 years old in the household
 - other: stressful life events; access to firearms



Suicide Risk Factors

SAD PERSONS

Sex (male)
Age > 60 years old
Depression
Previous attempts
Ethanol abuse
Rational thinking loss (delusions, hallucinations, hopelessness)
Suicide in family
Organized plan
No spouse (no support systems)
Serious illness, intractable pain

- psychiatric disorders
 - mood disorders (15% lifetime risk in depression; higher in bipolar)
 - anxiety disorders (especially panic disorder)
 - schizophrenia (10-15% risk)
 - substance abuse (especially alcohol – 15% lifetime risk)
 - eating disorders (5% lifetime risk)
 - adjustment disorder
 - conduct disorder
 - personality disorders (borderline, antisocial)
- past history
 - prior suicide attempt
 - family history of suicide attempt/completion

Clinical Presentation

- symptoms associated with suicide
 - hopelessness
 - anhedonia
 - insomnia
 - severe anxiety
 - impaired concentration
 - psychomotor agitation
 - panic attacks

Approach

Every Patient: “Have you had any thoughts of wanting to hurt/kill yourself?”

- ideation – “Do you have thoughts about ending your life, committing suicide?”
 - passive – would rather not be alive but does not admit to idea that involves act of initiation
 - ♦ e.g. “I’d rather not wake up,” “I wouldn’t mind if a car hit me”
 - active
 - ♦ e.g. “I think about killing myself”
- plan – “Do you have a plan as to how you would end your life?”
- intent – “You talk about wanting to die, but are you planning to do this?”, “What has stopped you from ending your life?”
- past attempts – highest risk if previous attempt in past year
 - ask about lethality, outcome, medical intervention

Assessment of Suicidal Ideation

- onset and frequency of thoughts – “When did this start? How often do you have these thoughts?”
- control over suicidal ideation – “Can you stop the thoughts or call someone for help?”
- lethality – “Do you want to end your life? Or get a ‘release’ from your emotional pain?”
- access to means – “How will you get a gun?” “Which bridge do you think you would go to?”
- time and place – “Have you picked a date and place? Is it in an isolated location?”
- provocative factors – “What makes you feel worse (e.g. being alone)?”
- protective factors – “What keeps you alive (e.g. friends, family, pets, faith, therapist)?”
- final arrangements – “Have you written a suicide note? Made a will? Given away your belongings?”
- practiced suicide or aborted attempts – “Have you put the gun to your head? Held the medications in your hand? Stood at the bridge?”
- ambivalence – “There must be a part of you that wants to live – you came here for help”

Assessment of Suicide Attempt

- setting – isolated vs. others present, chance of discovery
- planned vs. impulsive attempt, triggers/stressors
- intoxication
- medical attention – brought in by another person vs. brought in by self to ER
- time lag from suicide attempt to ER arrival
- expectation of lethality, dying
- reaction to survival – guilt/remorse vs. disappointment/self-blame

Management

- depends on the level of risk identified
- higher risk
 - patients with a plan, access to lethal means, recent social stressors, and symptoms suggestive of a psychiatric disorder should be hospitalized immediately
 - do not leave patient alone; remove potentially dangerous objects from room
 - if patient refuses to be hospitalized, complete form for involuntary admission
- lower risk
 - patients who are not actively suicidal, with no plan or access to lethal means
 - discuss protective factors and supports in their life, remind them of what they live for, promote survival skills that helped them through previous suicide attempts



Pharmacotherapy and Suicide Risk
Once antidepressant therapy is initiated, patients should be followed frequently as there is a “suicide window” in which the patient may still be depressed, but now has enough energy to carry out suicide. Avoid tricyclic antidepressants (TCAs) because of high lethality in overdose!



- Asking patients about suicide will not give them the idea or the incentive to commit suicide.
- The best predictor of completed suicide is a history of attempted suicide.
- The most common psychiatric disorders associated with completed suicide are mood disorders and alcohol abuse.

- make a safety plan – an agreement that they will not harm themselves, avoid alcohol, drugs, and situations that may trigger suicidal thoughts, follow-up with you at a designated time, and contact a health care worker, call a crisis line or go to an emergency department if they feel unsafe or if their suicidal feelings return or intensify
- depression: hospitalize if severe or if psychotic features are present; otherwise outpatient treatment with good supports and SSRIs/SNRIs
- alcohol-related: usually resolves with abstinence for a few days; if not, suspect depression
- personality disorders: crisis intervention/confrontation, may or may not hospitalize
- schizophrenia/psychosis: hospitalization
- parasuicide/self-mutilation: long-term psychotherapy with brief crisis intervention when necessary
- proper documentation of the clinical encounter and rationale for management is essential

Somatoform Disorders

General Characteristics

- physical signs and symptoms lacking a known medical basis in the presence of psychological factors that are judged to be important in the initiation, exacerbation, or maintenance of the disturbance
- cause significant distress or impairment in functioning
- symptoms are produced unconsciously
- symptoms are **not** the result of malingering or factitious disorder which are under conscious control
- primary gain: somatic symptom represents a symbolic resolution of an unconscious psychological conflict; serves to reduce anxiety and conflict; no external incentive
- secondary gain: the sick role; external benefits obtained or unpleasant duties avoided (e.g. work)

Management of Somatoform Disorders

- brief frequent visits
- limit number of physicians involved in care
- focus on psychosocial not physical symptoms
- minimize medical investigations; co-ordinate necessary investigations
- biofeedback
- psychotherapy: conflict resolution
- minimize psychotropic drugs: anxiolytics in short term only, antidepressants for depressive symptoms
- attend to transference and countertransference



Malingering – intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by external reward (e.g. avoiding work, obtaining financial compensation or obtaining drugs)

Factitious disorder – intentional production or feigning of physical or psychological signs or symptoms in order to assume the sick role where external incentives (e.g. economic gain) are absent



Conversion Disorder

- one or more symptoms or deficits affecting voluntary motor or sensory function that mimic a neurological or general medical condition (e.g. impaired co-ordination, local paralysis, double vision, seizures or convulsions)
- psychological factors thought to be etiologically related to the symptoms as the initiation of symptoms is preceded by conflicts or other stressors
- 11-300/100,000 in general population; focus of treatment in 1-3% of outpatient referrals to mental health clinics
- more common in rural populations and in individuals with little medical knowledge
- spontaneous remission in 95% of acute cases, 50% of chronic cases (>6 months)

Somatization Disorder

- recurring, multiple, clinically significant physical complaints which result in patient seeking treatment or having impaired functioning
- ≥8 physical symptoms that have no organic pathology including each of:
 - four pain symptoms related to at least four different sites or functions
 - two gastrointestinal symptoms, not including pain
 - one sexual symptom, not including pain
 - one pseudo-neurological symptom, not including pain (e.g. numbness, paresthesia)
- onset before age 30; extends over a period of years
- lifetime prevalence 0.2-2% among women and 0.2% among men
- cultural factors may influence sex ratio
- complications: anxiety, depression, unnecessary medications or surgery
- often a misdiagnosis for an insidious illness so rule out all organic illnesses (e.g. multiple sclerosis)

Pain Disorder

- pain is primary symptom and is of sufficient severity to warrant medical attention
- usually no organic pathology but when it exists, reaction is excessive
- lifetime prevalence 12%
- psychiatric disorders (mood, anxiety, substance) may precede, co-occur or result from pain disorder

Hypochondriasis



- preoccupation with fear of having, or the idea that one has, a serious disease based on a misinterpretation of one or more bodily signs or symptoms
- evidence does not support diagnosis of a physical disorder
- fear of having a disease despite medical reassurance
- belief is not of delusional intensity (as in delusional disorder, somatic type) as person acknowledges unrealistic interpretation
- duration is ≥ 6 months; onset in 3rd-4th decade of life
- community prevalence 1.1-4.5%; prevalence in general medical practice 4-9%; higher in psychiatric settings

Body Dysmorphic Disorder

- preoccupation with imagined defect in appearance or excess concern around slight anomaly
- usually related to face
- M=F, prevalence 1-2.2% in the community; 6-15% in dermatology/cosmetic surgery clinics
- may lead to avoidance of work or social situations

Dissociative Disorders

Definition

- dissociation so severe that the usually integrated functions of consciousness and perception of self break down
- sudden or gradual onset, transient or chronic course
- symptoms cause distress or impaired functioning

Manifestations

- dissociative amnesia, dissociative fugue, dissociative identity disorder, and depersonalization disorder
- differential diagnosis: PTSD, acute stress disorder, somatization disorder, substance abuse, general medical condition (e.g. complex/partial seizures)

Table 7. Dissociative Disorders

	Amnesia	Fugue	Identity Disorder	Depersonalization Disorder
Diagnosis	Inability to recall important personal information, usually of a traumatic or stressful nature; may be localized, selective or generalized	Sudden, unexpected travel away from home or workplace with inability to recall some or all of one's past; may assume new identity	Two or more distinct personalities that take control of an individual's behaviour; amnesia regarding personal history (a.k.a. Multiple Personality Disorder)	Persistent or recurrent experiences of feeling detached from one's mental processes or body (i.e. like being in a dream)
Epidemiology	6% prevalence Increased in survivors of trauma (war, abuse)	0.2% prevalence May occur under traumatic circumstances (combat, rape, natural disasters)	1.3% prevalence, M:F=1.3:9 May have history of physical or sexual abuse	Rare disorder Approximately 50% of adults have experienced a single brief episode of depersonalization, precipitated by extreme stress
Treatment	Psychotherapy, hypnosis No proven role for barbiturates/ pharmacologically-assisted interviewing	Usually spontaneous recovery Psychotherapy, hypnosis Ensure stability and safety No proven role for barbiturates/ pharmacologically-assisted interviewing	Three stages: symptom stabilization, attention to trauma, reintegration Psychotherapy, hypnosis Symptom-oriented adjuvants (antidepressants, anxiolytics) No proven role for barbiturates/ pharmacologically-assisted interviewing	Psychotherapy Pharmacotherapy: clonazepam, fluoxetine, clomipramine

Sleep Disorders

Criteria for Diagnosis

- causes significant distress or impairment in functioning
- not due to medications, drugs, or a GMC

Nocturnal Myoclonus

- middle-aged and elderly
- myoclonic jerks every 20-40 seconds
- bed partner complaints
- treatment: benzodiazepines (clonazepam, nitrazepam)

Narcolepsy

- irresistible sleep attacks (up to 30 minutes) and persistent day time drowsiness occurring daily for **≥3 months**
- cataplexy (sudden temporary episodes of paralysis with loss of muscle tone)
- sleep paralysis
- hypnagogic (while falling asleep)/hypnopompic (while waking) hallucinations are manifestations of recurrent invasions of rapid eye movement (REM) sleep into the transition between sleep and wakefulness
- incidence 4 in 10,000 cases; M=F
- treatment: stimulants (methylphenidate, D-amphetamine), TCAs, SSRIs

PRIMARY INSOMNIA

- see [Family Medicine](#), FM46

SLEEP APNEA

- see [Respirology](#), R32



Symptoms of Narcolepsy

CHAP

Cataplexy
Hallucinations
Attacks of Sleep
Paralysis on waking



Sexuality and Gender

Sexual Orientation

- describes the degree of a person's erotic attraction to people of the same sex, the opposite sex, or both sexes
- individuals may fall anywhere along a continuum between exclusive homosexuality and exclusive heterosexuality
- homosexual and bisexual individuals undergo a developmental process of identity formation
 - **sensitization** – sensation of being different from one's peers
 - **identity confusion** – after puberty, awareness of same-sex attraction may conflict with social expectations
 - **identity assumption** – self-definition as homosexual or bisexual, but not yet fully accepted
 - **commitment** – self-acceptance and comfort with identity; disclosure to family, social, occupational settings

Paraphilias

- **definition:** sexual arousal, fantasies, sexual urges or behaviour involving non-human objects, suffering or humiliation of oneself or one's partner, children or other non-consenting person
- **subtypes:** exhibitionism, fetishism, frotteurism, voyeurism, pedophilia, sexual masochism, sexual sadism, transvestite fetishism, not otherwise specified (NOS)
- rarely self-referred; come to medical attention through interpersonal or legal conflict
- person usually has more than one paraphilia; only 5% of paraphilia diagnoses attributed to women
- **typical presentation**
 - begins in childhood or early adolescence; increasing in complexity and stability with age
 - chronic, decreases with advancing age
 - may increase with psychosocial stressors
- **treatment**
 - anti-androgen drugs
 - behaviour modification
 - psychotherapy

Gender Identity Disorder

- gender identity is set at approximately 3 years of age
- **typical presentation**
 - strong and persistent cross-gender identification
 - repeated stated desire or insistence that one is of the opposite sex
 - preference for cross-dressing, cross-gender roles in make-believe plays
 - intense desire to participate in the stereotypical games and pastimes of the opposite sex
 - strong preference for playmates of the opposite sex
 - significant distress or impairment in functioning and persistent discomfort with his or her sex or gender role
- **treatment**
 - psychotherapy
 - hormonal therapy
 - sexual reassignment surgery

SEXUAL DYSFUNCTION

- see Gynecology, GY31 and Urology, U30

Eating Disorders



Epidemiology

- anorexia nervosa (AN) – 1% of adolescent and young adult females; onset 13-20 years old
- bulimia nervosa (BN) – 2-4% of adolescent and young adult females; onset 16-18 years old
- F:M=10:1; mortality 5-10%

Etiology

- multifactorial – psychological, sociological and biological associations
- **individual:** perfectionism, lack of control in other life areas, history of sexual abuse
- **personality:** obsessive-compulsive, histrionic, borderline
- **familial:** maintenance of equilibrium in dysfunctional family
- **cultural factors:** prevalent in industrialized societies, idealization of thinness in the media
- **genetic factors**
 - AN: 6% prevalence in siblings, with one study of twin pairs finding concordance in 9 of 12 monozygotic pairs versus concordance in 1 of 14 dizygotic pairs
 - BN: higher familial incidence of affective disorders than the general population

Risk Factors

- **physical factors:** obesity, chronic medical illness (e.g. diabetes mellitus)
- **psychological factors:** individuals who by career choice are expected to be thin, family history (mood disorders, eating disorders, substance abuse), history of sexual abuse, homosexual males, competitive athletes, concurrent associated mental illness [depression, OCD, anxiety disorder (especially panic and agoraphobia), substance abuse (BN)]

Anorexia Nervosa

DSM-IV-TR Diagnostic Criteria for Anorexia Nervosa

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- refusal to maintain body weight at or above a minimally normal weight for age and height (e.g. weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected)
- intense fear of gaining weight or becoming fat, even though underweight
- disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight
- in postmenarcheal females, amenorrhea, i.e. the absence of at least three consecutive menstrual cycles

Specific Type

- **restricting:** during the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behaviour (i.e. self-induced vomiting or the misuse of laxatives, diuretics, or enemas)
- **binge-eating/purging:** during the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behavior (i.e. self-induced vomiting or the misuse of laxatives, diuretics, or enemas)



Athletic Triad
 1. Disordered eating
 2. Amenorrhea
 3. Osteoporosis

Associated Features

- deteriorating mood (irritable, anxious, extreme sensitivity, sadness)
- isolation
- trouble concentrating due to repetitive, intrusive, irresolvable and anxiety provoking thoughts about food and weight
- malnutrition
- poor sleep

Management

- criteria for admission vary among hospitals
- admit to hospital if: <65% of standard body weight (<85% of standard body weight for adolescents), hypovolemia requiring intravenous fluid, heart rate <40 bpm, abnormal serum chemistry or if actively suicidal
- agree on target body weight on admission and reassure this weight will not be surpassed
- psychotherapy (individual/group/family): addressing food and body perception, coping mechanisms, health effects
- monitor for complications of AN (see Table 8)
- monitor for **refeeding syndrome**:
 - a potentially life-threatening metabolic response to refeeding in severely malnourished patients resulting in severe shifts in fluid and electrolyte levels
 - complications include hypophosphatemia, congestive heart failure, cardiac arrhythmias, delirium and death
 - prevention: slow refeeding, gradual increase in nutrition, supplemental phosphorus, close monitoring of electrolytes and cardiac status

Prognosis

- early intervention much more effective
- with treatment, 70% resume a weight of at least 85% of expected levels and about 50% resume normal menstrual function
- eating peculiarities and associated psychiatric symptoms are common and persistent
- long-term mortality – 10% to 20% of patients hospitalized will die in next 10 to 30 years (secondary to severe and chronic starvation, metabolic or cardiac catastrophes, with a significant proportion committing suicide)

Bulimia Nervosa

DSM-IV-TR Diagnostic Criteria for Bulimia Nervosa

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- recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following
 - eating, in a discrete period of time, an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances
 - a sense of lack of control over eating during the episode (e.g. a feeling that one cannot stop eating or control what or how much one is eating)
- recurrent inappropriate compensatory behaviour in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, enemas, or other medications, fasting, or excessive exercise
- the binge eating and inappropriate compensatory behaviours both occur, on average, at least twice a week for 3 months
- self-evaluation is unduly influenced by body shape and weight
- the disturbance does not occur exclusively during episodes of Anorexia Nervosa

Specific Type

- **purging**: during the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas
- **non-purging**: during the current episode of bulimia nervosa, the person has used other inappropriate compensatory behaviours, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas

Associated Features

- fatigability and muscle weakness due to repetitive vomiting and fluid/electrolyte imbalance
- tooth decay
- swollen appearance around angle of jaw and puffiness of eye sockets due to fluid retention
- reddened knuckles, Russell's sign (knuckle callus from self-induced vomiting)
- trouble concentrating
- weight fluctuation over time

**Ipecac Syrup**

- Was commonly used to induce vomiting in accidental poisoning or drug overdose.
- Used chronically by some patients with EDs to induce vomiting.

Management

- criteria for admission: significant electrolyte abnormalities
- biological
 - treatment of starvation effects
 - SSRIs
- psychological
 - develop trusting relationship with therapist to explore personal etiology and triggers
 - reality-oriented feedback, cognitive behavioural therapy, family therapy
 - recognition of health risks
- social
 - challenge destructive societal views of women
 - use of hospital environment to provide external patterning for normative eating behaviour

Prognosis

- few recover without recurrence
- good prognostic factors: onset before age 15, achieving a healthy weight within 2 years of treatment
- poor prognostic factors: later age of onset, previous hospitalizations, individual and familial disturbance

Table 8. Physiologic Complications of Eating Disorders

System	Starvation/Restriction	Binge-Purge
General	Low BP, low HR, significant orthostatic changes ± syncopal episodes, low temperature, vitamin deficiencies	Russell's sign (knuckle callus) Parotid gland enlargement Perioral skin irritation Periocular and palatal petechiae Loss of dental enamel and caries Aspiration pneumonia Metabolic alkalosis secondary to hypokalemia and loss of acid
Endocrine	Primary or secondary amenorrhea, decreased T3/T4	
Neurologic	Grand mal seizure (decreased Ca, Mg, PO ₄)	
Cutaneous	Dry skin, lanugo hair, hair loss or thinning, brittle nails, yellow skin from high carotene	
GI	Constipation, GERD, delayed gastric emptying	Acute gastric dilation/rupture, pancreatitis, GERD, hematemesis secondary to Mallory-Weiss tear
CVS	Arrhythmias, CHF	Arrhythmias, cardiomyopathy (from use of ipecac), sudden cardiac death (decreased K)
MSK	Osteoporosis secondary to hypogonadism	Muscle wasting
Renal	Pre-renal failure (hypovolemia), renal calculi	Renal failure (electrolyte disturbances)
Extremities	Pedal edema (decreased albumin)	Pedal edema (decreased albumin)
Lab Values	Starvation: decreased RBCs, decreased WBCs, decreased LH, decreased FSH, decreased estrogen, decreased testosterone, increased growth hormone, increased cholesterol Dehydration: increased BUN	Vomiting: decreased Na, decreased K, decreased Cl, decreased H, increased amylase; hypokalemia with metabolic alkalosis Laxatives: decreased Na, decreased K, decreased Cl, increased H; metabolic acidosis

Personality Disorders

General Diagnostic Criteria

- an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual's culture; manifested in two or more of: cognition, affect, interpersonal functioning, impulse control
- inflexible and pervasive across a range of situations
- causes distress or impaired functioning not necessarily for the person with the personality disorder, but for those around him/her
- pattern is stable and well established by adolescence or early adulthood
- associated with many complications, such as depression, suicide, violence, brief psychotic episodes, multiple drug use and treatment resistance
- each personality disorder is present in 1% of the population
- personality disorders are lifelong and chronic
- the mainstay of treatment is psychotherapy with the addition of pharmacotherapy to treat associated axis I disorders (i.e. depression, anxiety, substance abuse)



Screening for Personality Disorders

I'd like to ask some questions about your thoughts and feelings to get to understand what you're usually like.

1. Marked shifts in mood: How often is it that your mood will change drastically over the course of a day, with sudden shifts from feeling your normal self to feelings of depression, irritability or anger? How long has this been going on?

2. Uncomfortable when not centre of attention: Some people like to be the centre of attention and others don't mind blending into the background. How do you describe yourself? What's it like for you when you're not the centre of attention?

3. Actions directed towards immediate satisfaction: Do you get frustrated if you can't have what you want right away, even if waiting a little longer would get you something even better? Do you get excited about an idea, make big plans and then lose interest before it gets off the ground?

4. Reluctant to confide in others because of unwarranted fears: Do you prefer that people don't get to know you too well? For what reasons? Do you wonder if certain friends and acquaintances are not very loyal or trustworthy? What makes you concerned?


5. Excessive social anxiety: Do you worry about embarrassing yourself in front of other people, like saying the wrong thing at a gathering? Does it stop you from starting a conversation? How often are you the one to introduce yourself? Eventually will you relax and start to open up in a social situation?

6. Unwilling to get involved with people unless certain of being liked: How often do you hold back from getting to know someone because you're concerned they might not like you? Does this limit your number of friends?

Yes to 2+ questions = 80% chance of PD.

Table 9. Classification and Diagnosis of Personality Disorders

Note: For each personality disorder, the most recognizable feature is indicated in *italics*

Diagnostic Cluster	Diagnosis
Cluster A "Mad" Patients seem odd, eccentric, withdrawn Familial association with psychotic disorders Common defense mechanisms: intellectualization, projection, magical thinking	Paranoid Personality Disorder (0.5-3%) <i>Pervasive distrust and suspiciousness of others, interpret motives as malevolent.</i> Blame problems on others and seem angry and hostile. Diagnosis requires 4 of: 1. Suspicious that others are exploiting or deceiving them 2. Pre-occupied with trustworthiness of acquaintances 3. Reluctant to confide in others 4. Interpret benign remarks as threatening, demeaning 5. Holds grudges 6. Perceives attacks on character and is quick to counterattack 7. Questions fidelity of partner without justification Schizoid Personality Disorder <i>Neither desires nor enjoys close relationships including being a part of a family; prefers to be alone.</i> <i>Lifelong pattern of social withdrawal</i> <i>Seen as eccentric and reclusive with restricted affect.</i> Diagnosis requires 4 of: 1. Does not enjoy or desire close relationships 2. Chooses solitary activities 3. Little to no interest in sexual activity with others 4. Takes pleasure in few (if any) activities 5. Few or no close friends 6. Indifference to praise or criticism 7. Emotionally cold, detached, or have flattened affect
Cluster B "Bad" Patients seem dramatic, emotional, inconsistent Familial association with mood disorders Common defense mechanisms: denial, acting out, regression (histrionic PD), splitting (borderline PD), projective identification, idealization/devaluation	Schizotypal Personality Disorder (3-5.6%) <i>Pattern of eccentric behaviours, peculiar thought patterns.</i> Diagnosis requires 5 of: 1. Ideas of reference 2. Odd beliefs, magical thinking (inconsistent with cultural norms i.e. belief in telepathy, superstitions) 3. Unusual perceptual experiences (i.e. bodily illusions) 4. Suspiciousness 5. Inappropriate or restricted affect 6. Odd, eccentric appearance or behaviour (i.e. involved in cults, strange religious practices) 7. Few close friends 8. Odd thinking, odd speech (i.e. vague, stereotyped) 9. Excessive social anxiety Narcissistic Personality Disorder (2%) <i>Sense of superiority, needs constant admiration, lacks empathy, but with fragile sense of self.</i> <i>Consider themselves "special" and will exploit others for personal gain.</i> Diagnosis requires 5 of: 1. Exaggerated sense of self-importance (grandiosity) 2. Preoccupied with fantasies of unlimited success, power, beauty, love 3. Believes he/she is "special" and should associate with other "special" people 4. Requires excessive admiration 5. Sense of entitlement 6. Takes advantage of others 7. Lacks empathy 8. Envious of others or believes that others are envious of him/her 9. Arrogant attitudes Histrionic Personality Disorder (1.3-3%) <i>Attention-seeking behaviour and excessively emotional. Are dramatic, flamboyant and extroverted. Cannot form meaningful relationships. Often sexually inappropriate.</i> Diagnosis requires 5 of: 1. Not comfortable unless centre of attention 2. Inappropriately sexually seductive 3. Uses physical appearance to attract attention 4. Speech is impressionistic, lacks detail 5. Theatrical and exaggerated expression of emotion 6. Easily influenced by others 7. Perceives relationships as more intimate than they actually are
 Borderline Personality IMPULSIVE Impulsive Moody Paranoid under stress Unstable self image Labile intense relationships Suicidal Inappropriate anger Vulnerable to abandonment Emptiness	Borderline Personality Disorder (2-4%) <i>Unstable moods and behaviour, feel alone in the world, problems with self image</i> <i>History of repeated suicide attempts, self-harm behaviours</i> <i>**10% suicide rate**</i> Diagnosis requires 5 of: 1. Frantic efforts to avoid real or imagined abandonment 2. Unstable and intense relationships 3. Unstable sense of self 4. Impulsivity in two potentially harmful ways (sexual, drugs, spending) 5. Recurrent suicidal behaviour/self-harm 6. Unstable mood/affect 7. General feelings of emptiness 8. Difficulty controlling anger 9. Transient dissociative symptoms or paranoid ideation associated with stress Antisocial Personality Disorder (M3%, F1%) <i>Lack of remorse for actions, manipulative and deceitful, often violate the law. May appear charming on first impression.</i> <i>Pattern of disregard for others and violation of rights of others must be present before the age of 15, however, for the diagnosis of ASPD patients must be at least 18.</i> Diagnosis requires 3 of the following: 1. Failure to conform to social norms by committing unlawful acts 2. Deceitfulness, lying, manipulating others for personal gain 3. Impulsive, fails to plan ahead 4. Irritable, aggressive, repeated fights or assaults 5. Recklessness and disregard for personal safety, safety of others 6. Irresponsible, cannot sustain work 7. Lack of remorse for actions
Cluster C "Sad" Patients seem anxious, fearful Familial association with anxiety disorder Common defense mechanisms: isolation, avoidance, hypochondriasis	Avoidant Personality Disorder (0.5-1.6%) <i>Timid and socially awkward with a pervasive sense of inadequacy and fear of criticism.</i> <i>Fear of embarrassing or humiliating themselves in social situations so remain withdrawn and socially inhibited.</i> Diagnosis requires 4 of: 1. Avoids occupational activities that involve significant interpersonal contact for fear of criticism or rejection 2. Unwilling to get involved with people unless certain of being liked 3. Restrained in intimate relationships for fear of being shamed or ridiculed 4. Preoccupied with being rejected or criticized in social situations 5. Inhibited in new interpersonal situations due to fear of inadequacy 6. Views him or herself as inferior, socially inept or personally unappealing 7. Reluctant to engage in new activities for fear of embarrassment Dependent Personality Disorder (1.6-6.7%) <i>Pervasive and excessive need to be taken care of, excessive fear of separation, clinging and submissive behaviours.</i> <i>Difficulty making everyday decisions.</i> Diagnosis requires 5 of: 1. Difficulty making everyday decisions without advice and reassurance from others 2. Needs others to assume responsibility for most major areas of his/her life 3. Difficulty expressing disagreement 4. Difficulty initiating projects due to lack of self-confidence 5. Goes to excessive lengths to obtain support 6. Uncomfortable or helpless when alone because of fear of being unable to take care of him/herself 7. Urgently seeks another relationship as a source of care and support when a close relationship ends 8. Unrealistically preoccupied with fears of being left to take care of him/herself Obsessive-Compulsive Personality Disorder (3-10%) <i>Preoccupation with orderliness, perfectionism, and mental and interpersonal control.</i> <i>Is inflexible, closed-off, and inefficient.</i> Diagnosis requires 4 of: 1. Preoccupation with details, rules, lists, order, organization, or schedules to extent that point of activity is lost 2. Perfectionism interferes with task completion 3. Excessively devoted to work to the exclusion of leisure activities and friendships 4. Inflexible about morality/ethics/values 5. Unable to discard worthless objects of no sentimental value 6. Reluctant to delegate tasks to others 7. Miserly spending style (money is hoarded for future disasters) 8. Rigid and stubborn

A key distinction between obsessive compulsive disorder (OCD) and obsessive compulsive personality disorder (OCPD) is that in OCD the symptoms are ego-dystonic (i.e. the patient realizes the obsessions are not reasonable) whereas in OCPD the symptoms are ego-syntonic (i.e. consistent with the patient's way of thinking).

Child Psychiatry

The Child Psychiatric Interview

- ID
 - name, age, family situation, school grade
- chief complaint
 - onset, time course, stressors, impact on child's and family's functioning, supports
 - child's functioning and behaviour at home, at school, and with peers
 - mental status (see adult mental status exam)
- history of present illness
 - symptoms and features of most likely diagnostic area (e.g. disruptive behaviour disorders (ADHD, CD, ODD), developmental disorders, learning disorders, abuse, mood disorders, and anxiety disorders)
 - in adolescents, consider psychotic disorders, eating disorders, and substance abuse disorders
 - screen for comorbid conditions
- risk assessment
 - physical/sexual abuse, suicidality, aggression/homicidality, firesetting, risky behaviour
 - past assessments (e.g. psychiatric, psychological, educational), treatments, risk issues (past suicide attempts, past aggression), previous contact with child protection services
 - brief developmental history – pregnancy, birth, milestones, general behaviour, parents' method of discipline, school functioning, peer relationships



HEADSSS Interview
 Home environment
 Education/Employment
 Activities
 Drugs/Diet
 Sex
 Safety
 Suicide/depression

Developmental Concepts

Table 10. Developmental Stages

Freud	Erikson	Piaget
Oral	Trust/mistrust (birth-1 year)	Sensorimotor (birth-2 years old)
Anal	Autonomy/shame, doubt (1-3 years old)	Object permanence (15 months) – Child begins to understand the concept that objects exist even when not visible Object constancy (18 months) – Child becomes comfortable with mother's absence by internalizing her image and the knowledge she will return
Oedipal	Initiative/guilt (4-6 years old)	Preoperational (2-7 years old)
Latency	Industry/inferiority (6-12 years old) Identity/role confusion (adolescence) <i>Erikson stages continue throughout life:</i> Intimacy/isolation (young adult) Generativity/stagnation (middle age) Integrity/despair (later life)	Concrete operations (7-11 years old) Formal operations (11+ years)

- **temperament:** innate psycho-physiological and behavioural characteristics of a child (e.g. emotionality, activity, and sociability); spectrum from “difficult” to “slow-to-warm-up” to “easy temperament”, plotted on nine parameters:
 - activity level, adaptation, attention span and persistence, distractibility, intensity of reaction, quality of mood, response to a new stimulus, rhythmicity, threshold of responsiveness
- **parental fit:** the congruence between parenting style (authoritative, authoritarian, permissive) and child's temperament
- **attachment:** special relationship between child and primary caretaker(s); develops during first year (see Table 11), best predictor of a child's attachment style is their parent's attachment style
- **stranger anxiety** (8 months): infants cry at approach of stranger
- **separation anxiety** (10-18 months): separation from attachment figure results in distress

Table 11. Attachment Models

Parent/Caregiver	Attachment Type	Features in Child
Loving, consistently available, sensitive, and receptive	Secure	Able to use caregiver to calm self
Rejecting, unavailable psychologically, insensitive responses	Insecure (avoidant)	Not reliant on caregiver for soothing
Inconsistent, insensitive responses, role reversal	Insecure (ambivalent/resistant)	
Frightening, dissociated, sexualized, or atypical	Disorganized	



Attachment type can be assessed in infants 10-18 months of age using the Strange Situation test, in which the child is stressed by the caregiver being removed from the situation and the stranger staying. Attachment style is measured by the child's behaviour during the reunion with the caregiver.



Attachment problems may present as a child who is difficult to soothe, has difficulty sleeping, problems feeding, tantrums or behaviours.



Health Canada advises Canadians under the age of 18 to consult physicians if they are being treated with SSRIs, SNRIs or mirtazapine. This request was made as a result of international reports that some of these drugs may be associated with an increased risk of suicidal ideation in patients under the age of 18. There was no increased risk of suicide completion.

Selective Serotonin Reuptake Inhibitors in Childhood Depression: Systematic Review of Published versus Unpublished Data

Lancet 2004; 363:1341-45

Study: Meta-analysis of data from 5 randomised controlled trials that evaluated SSRI vs. Placebo that were published or unpublished.

Patients: Age 5-18 diagnosed with depression.

Outcomes: Remission, response to treatment, depressive symptom scores, adverse events, suicide-related behaviors, and discontinuation of treatment because of adverse events.

Intervention: Fluoxetine, paroxetine, sertraline, citalopram, and venlafaxine.

Results: Fluoxetine has favourable risk-benefit profile, supported by published and unpublished data. Paroxetine and sertraline have weak-positive risk-benefit profiles by published data, and greater risk than benefit by unpublished data.

Fluoxetine, Cognitive-Behavioral Therapy and Their Combination for Adolescents with Depression: Treatment for Adolescents with Depression Study (TADS) Randomized Controlled Trial

JAMA 2004; 292(7):807-820

Study: Randomized controlled trial at 13 US academic and community clinics b/w spring 2000-summer 2003.

Patients: 439 patients ages 12-17 with a primary DSM IV diagnosis of major depressive disorder.

Outcomes: Children's Depression Rating Scale-Revised (CDRSR) total score.

Interventions: 12 weeks of (1) fluoxetine (10-40mg/d), (2) CBT, (3) CBT + fluoxetine (10-40mg/d), or (4) placebo.

Results: Fluoxetine with CBT had a statistically significant CDRSR score as compared to placebo ($P=0.001$) with a 71% response rate. This combo was greater than fluoxetine alone ($P=0.02$), and CBT alone ($P=0.01$). Fluoxetine alone was greater than CBT alone ($P=0.01$).

Mood Disorders

MAJOR DEPRESSIVE DISORDER

Epidemiology

- pre-pubertal 1-2%; post-pubertal 4-8%; F:M = 2:1

Clinical Presentation

- see *Adult Mood Disorders*, PS7
- more cognitive and fewer vegetative symptoms than adults
- physical factors: insomnia (children), hypersomnia (adolescents), somatic complaints, substance abuse
- psychological factors: boredom, irritability, anhedonia, discouragement, helplessness, low self-esteem, deterioration in academic performance, social withdrawal, lack of motivation
- comorbid diagnoses of anxiety, ADHD, conduct disorder, and eating disorders

Treatment

- majority never seek treatment
- individual (CBT, IPT)/family psychotherapy and education, modified school program
- SSRIs, SNRIs (see below)
- ECT: only in adolescents
- light therapy, self-help books

Prognosis

- prolonged, up to 1-2 years
- adolescent onset predicts chronic mood disorder; up to 2/3 will have another depressive episode within 5 years
- complications
 - negative impact on family and peer relationships
 - school failure
 - significantly increased risk of suicide attempt (10%) or completion
 - substance abuse

BIPOLAR DISORDER

Clinical Presentation

- see adult bipolar disorder/mania (DSM-IV-TR)
- mixed presentation more common in adolescent population than adult population
- unipolar depression may be an early sign of adult bipolar disorder
 - ~30% of psychotic depressed adolescents receive a bipolar diagnosis within 2 years of presentation
 - associated with rapid onset of depression, psychomotor retardation, mood-congruent psychosis, affective illness in family, pharmacologically induced mania

Treatment

- 1st line: mood stabilizers ± antipsychotics
- 2nd line: antidepressants, benzodiazepines (careful of disinhibiting effect)

Anxiety Disorders

- prevalence 2-15%; F:M = 2:1

Diagnosis

- school problems, recurrent physical symptoms (stomach aches, headaches) especially in mornings, social and relationship problems, social withdrawal and isolation, family conflict, irritability and mood symptoms, alcohol and drug use in adolescents

Treatment

- family psychotherapy
- behaviour modification techniques, stress reduction, parental education, predictive and supportive environment, relaxation techniques
- pharmacotherapy: SSRIs (e.g. fluoxetine), benzodiazepines (e.g. clonazepam – use with caution, may have disinhibiting effect)
 - fluvoxamine and sertraline also have good evidence, particularly for OCD

SEPARATION ANXIETY DISORDER

Epidemiology

- prevalence: 4% of children/adolescents
- on average 7.5 years old at onset, 10 years old at presentation
- common for mother to have an anxiety or depressive disorder

Differential Diagnosis

- simple or social phobia, depression, learning disorder, truancy, conduct disorder, school-related problems (e.g. bullying)

Clinical Presentation

- school refusal (75%)
- excessive and developmentally inappropriate anxiety on separation from primary caregiver with physical or emotional distress for at least two weeks
- persistent worry, refusal to sleep, clinging, nightmares, somatic symptoms
- comorbid major depression common (2/3)
- worry about something happening to parent or themselves

Prognosis

- if inadequately treated early on, may present later in a more severe form
- may develop into panic disorder with/without agoraphobia

SOCIAL ANXIETY DISORDER

- must distinguish between shy child and child with social anxiety
 - diagnosis only if anxiety interferes significantly with daily routine, social life, academic functioning, or if markedly distressed
- features: temper tantrums, freezing, clinging behaviour, mutism, excessively timid, stays on periphery, refuses to be involved in group play
- must be capable of developing social relationships
- must occur in settings with peers, not just adults
- selective mutism:
 - does not speak in front of others; no problems speaking at home
 - must rule out language or communication problems
 - severe form of social anxiety



The shy child is quiet and reluctant to participate but slowly 'warms up'.

POST-TRAUMATIC STRESS DISORDER (PTSD)

- diagnostic criteria same as adults (see PS15)
 - in children, one often sees repetitive play involving the event, generalized nightmares, psychosomatic symptoms, omen formation
- common examples of trauma include: sexual/physical abuse, witnessing family violence, natural disasters
- can also be associated with onset of sexual activity

OBSESSIVE-COMPULSIVE DISORDER (OCD)

- diagnostic criteria same as adults, except it is not necessary for child to recognize thoughts or actions as excessive or unreasonable (see PS15)
- 0.3-1% of children/adolescents; tends to begin earlier in boys than girls
 - tend to engage in rituals at home rather than in front of others
 - associated with Tourette's Disorder, tics, and ADHD

PANIC DISORDER

- diagnostic criteria same as adults (see PS13)
- genetic/parental modeling/identification hypothesized as cause
- often parent with panic or depressive disorder

GENERALIZED ANXIETY DISORDER (GAD)

- diagnostic criteria same as adults (see PS13)
- often redo tasks, show dissatisfaction with their work and tend to be perfectionistic
- often require reassurance and support to take on new tasks

SPECIFIC PHOBIA

- common phobias in childhood include a fear of heights, small animals, doctors, dentists, darkness, loud noises, thunder and lightning

Childhood Schizophrenia

Epidemiology

- 1/2,000 in childhood; increases after puberty to adult rates (1%) in late adolescence
- diagnostic criteria same as in adults (see PS4)
- <6 years old may present in similar fashion to autism prior to onset of core symptoms
- prognosis poor as cognitive, language, social and personality development are disrupted

Treatment

- psychotherapy, family education
- low dose antipsychotics for target behaviours (i.e. aggression, hyperactivity, impulsiveness)
- hospitalization or residential placement, if severe

Pervasive Developmental Disorders (PDD)

- include autism, asperger's, childhood disintegrative disorder, Rett's disorder, and PDD NOS (not otherwise specified)
- M:F = 3-4:1 (except for Rett's with female predominance)

Differential Diagnosis

- mental retardation, childhood schizophrenia, social phobia, OCD, communication disorder, non-verbal learning disorder, ADHD, abuse, hearing or visual impairment, seizure disorder, motor impairment

Management

- hearing test to rule out impairment
- psychological testing to assess intellectual functioning and learning
- chromosomal analysis to rule out abnormalities (e.g. trisomy 21, fragile X syndrome)
- rule out psychotic disorders, social problems, depression, anxiety, abuse

Treatment

- team-based: school, psychologist, occupational therapist, physiotherapist, speech and language therapy, audiology, pediatrics, psychiatry
- family education and support
- treat concomitant disorders such as tics, OCD, anxiety, depression, and seizure disorder
- behaviour management, school programming
- pharmacotherapy: atypical antipsychotics (for bizarre behaviours, agitation, self-mutilation, tics), SSRIs (for anxiety, depression), stimulants (for associated hyperactivity)

Prognosis

- variable, but improves with early intervention
- better if IQ >60 and able to communicate

AUTISM

- prevalence 1/1,000
- abnormalities in three areas
 - **social interaction** – impaired non-verbal behaviours (eye contact, facial expression, hand gestures), failure to develop appropriate peer relationships, lack of social/emotional reciprocity
 - **communication** – delayed or absent speech or marked impairment to initiate or sustain a conversation; stereotyped/repetitive or idiosyncratic use of language; absence of appropriate make-believe play
 - **restricted and repetitive behaviours, interests, and activities** – inflexible adherence to specific, non-functional routines, stereotyped hand or body movements (e.g. rocking)
- at least 6 features before 3 years old (at least 2 from social interaction and 1 from other 2 categories)

ASPERGER'S DISORDER

- prevalence 3/1,000
- no early speech and language delay, no cognitive deficits, normal to high intelligence
- impaired social interaction with ≥ 2 of
 - nonverbal interactions, peer relationships, spontaneous sharing of enjoyment/activities, social/emotional reciprocity
- restricted repetitive patterns of behaviour/interests with >1 of
 - restricted interest with high intensity, inflexible nonfunctional routines, repetitive mannerisms, preoccupation with parts
- causes impairment, no delay in language or cognitive development, not caused by another PDD

CHILDHOOD DISINTEGRATIVE DISORDER (CDD)

- similar to autism, but there must be a period of at least 2 years (and up to ten years) of normal development
- rule out degenerative brain disease, schizophrenia

RETT'S DISORDER

- X-linked dominant disorder, therefore predominantly in girls
- restriction of brain growth beginning in first year of life
- normal development between 6 months to 4 years, then regression (loss of purposeful hand movements, mental retardation, seizures, neurological, respiratory and motor deficits)

PDD NOS

- marked deficits in above areas, but does not meet full criteria for another PDD



	Rett's	CDD
Development	Normal development and head size until ≥ 5 months	Normal development for ≥ 2 years
Incidence	6-7/100,000 females	1/100,000 boys > girls
Deficits	Decreased head growth, hand movements, skills (social, coordination, language)	Decreased skills (language, social, motor), bowel/bladder control, play

Attention Deficit Hyperactivity Disorder (ADHD)

- prevalence: 5-12% of school-aged children; M:F = 4:1, although girls may be under-diagnosed
- girls tend to have inattentive/distractible symptoms; boys have impulsive/hyperactive symptoms

Etiology

- genetic – dopamine candidate genes, catecholamine/neuroanatomical hypothesis
- cognitive – MR, inhibitory control and other errors of executive function
- arousal – alterations in the sensory system filters

Diagnosis

- differential: learning disorders, hearing/visual defects, thyroid, atopic conditions, congenital problems (FAS, Fragile X), lead poisoning, history of head injury, traumatic life events (abuse)
- diagnosis (using Conner's Teacher's and Parent's ADHD Scales)
 - **six or more** symptoms of inattention and/or hyperactivity-impulsivity persisting for at least **6 months**
 - onset **before age 7**
 - symptoms present in at least **two settings** (i.e. home, school, work)
 - interferes with academic, family, and social functioning
 - does not occur exclusively during the course of another psychiatric disorders



Observe child for **"ATTENTION"** features:
Annoying
Temperamental
Energetic
Noisy
Task incompletion
Inattentive
Oppositional
Negativism

Table 12. Core Symptoms of ADHD (DSM-IV)

Inattention	Hyperactivity	Impulsivity
Careless mistakes	Fidgets, squirms in seat	Blurts out answers before questions completed
Cannot sustain attention in tasks or play	Leaves seat when expected to remain seated	Difficulty awaiting turn
Does not listen when spoken to directly	Runs and climbs excessively	Interrupts/intrudes on others
Fails to complete tasks	Cannot play quietly	
Disorganized	On the "go", driven by a motor	
Avoids, dislikes tasks that require sustained mental effort	Talks excessively	
Loses things necessary for tasks or activities		
Distractible		
Forgetful		

Features

- average onset 3 years old
- identification upon school entry
- rule out developmental delay, genetic syndromes, encephalopathies or toxins (alcohol, lead)
- risk of substance abuse, particularly cannabis and cocaine, depression, anxiety, academic failure, poor social skills, risk of comorbid CD and/or ODD, risk of adult ASPD
- associated with family history of ADHD, difficult temperamental characteristics

Treatment

- non-pharmacological: parent management, anger control strategies, positive reinforcement, social skills training, individual/family therapy, resource room, tutors, classroom intervention, exercise routines, extracurricular activities
- pharmacological
 - standard treatment: stimulants (methylphenidate – Ritalin®, Concerta® [long-acting]; dextroamphetamine; mixed amphetamine salts – Adderall®), SNRI (atomoxetine – Strattera®)
 - for comorbid symptoms: antidepressants, antipsychotics

A 14-month Randomized Clinical Trial of Treatment Strategies for Attention-Deficit/Hyperactivity Disorder
Arch Gen Psychiatry 1999; 56:1073-1086
Purpose: To investigate the long-term efficacy of pharmacotherapy and behaviour therapy, as well as their combination.
Study Characteristics: Single blinded RCT with 579 children, and 14 month follow-up.
Participants: Age 7-9.9 with characteristics typical of other ADHD samples.
Intervention: 14 months of one of four interventions: 1) medical management, with methylphenidate used as a first line agent, followed by other drugs as required, and monthly follow-up; 2) intensive behavioural therapy (parent, school, and child); 3) the two combined; or 4) standard community care.
Main Outcomes: ADHD symptoms, oppositional/aggressive symptoms, social skills, internalizing symptoms (anxiety and depression), parent-child relation, and academic achievement
Results: All groups showed a reduction in symptoms over time. Medication was found to be superior to behavioural treatment for ADHD symptoms, but no other outcomes. Combined treatment and medication did not differ significantly across any domain in direct comparison. MTA medication treatments were superior to community care, despite the fact that two-thirds of community-treated subjects received medication during the study period.
Conclusions: Use of psychostimulant medications is superior to behavioural interventions or community care in treating ADHD symptoms. Combined medical and behavioural treatment is not more efficacious than medication alone in treating ADHD symptoms.

Prognosis

- 65% continue into adulthood; secondary personality disorders and compensatory anxiety disorders are identifiable
- 70-80% continue into adolescence, but hyperactive symptoms usually abate

Oppositional Defiant Disorder (ODD)

- prevalence: 2-16%

Diagnosis

- pattern of negativistic/hostile and defiant behaviour for ≥ 6 months with ≥ 4 of
 - loses temper, argues with adults, defies adult rules, deliberately annoys, blames others, touchy/easily annoyed, angry and resentful, spiteful or vindictive
- behaviour causes significant impairment in social, academic or occupational functioning
- behaviours do not occur exclusively during the course of a psychotic or mood disorder
- criteria not met for CD; if 18 years or older, criteria not met for ASPD
- features that typically differentiate ODD from transient developmental stage: onset < 8 years, chronic duration (> 6 months), frequent intrusive behaviour
- impact of ODD: poor school performance, few friends, strained parent/child relationships
- may progress to CD

Treatment

- establish boundaries
- parent management training and psychoeducation
- individual/family therapy
- pharmacotherapy for comorbid disorders
- school/daycare interventions to help with behaviour management

Conduct Disorder (CD)

- prevalence: 1.5-3.4% (M:F = 4-12:1)

Etiology

- parental/familial factors – parental psychopathology (e.g. ASPD, substance abuse), child rearing practices (e.g. child abuse, discipline), low SES, family violence
- child factors – difficult temperament, ODD, learning problems, neurobiology

Diagnosis

- differential: ADHD, depression, head injury, substance abuse
- diagnosis: use multiple sources (Achenbach Child Behavioural Checklist, Teacher's Report Form)
 - pattern of behaviour that violates rights of others and age appropriate social norms with ≥ 3 in past 12 months and ≥ 1 in past 6 months:
 - ♦ aggression to people and animals (bullying, physical fights, use of weapons, forced sex)
 - ♦ destruction of property, firesetting with intent to damage
 - ♦ deceitfulness or theft (breaking and entering, car theft)
 - ♦ violation of rules (out all night before 13, runaway ≥ 2 times or for long periods of time, often truant from school before 13)
 - disturbance causes clinically significant impairment in social, academic or occupational functioning
 - if individual is 18 years or older, criteria not met for antisocial personality disorder
- diagnostic types
 - childhood onset: at least one criterion prior to age 10
 - ♦ poor prognosis: associated with ODD, aggressiveness, impulsiveness
 - adolescent onset: absence of any criteria until age 10
 - ♦ better prognosis; least aggressive, gang-related delinquency
 - mild, moderate, severe

Treatment

- early intervention necessary and more effective, long-term follow-up required
- parent management training, anger replacement training, CBT, family therapy, education/employment programs, social skills training, medications for aggressiveness or comorbid disorders
- pharmacotherapy is insufficient; mainly used for treatment of comorbid disorders

Prognosis

- poor prognostic indicators include early-age onset, high frequency and variety of behaviours, pervasiveness (i.e. in home, school, community), comorbid ADHD, early sexual activity, substance abuse
- 50% of CD children become adult ASPD

**ODD kids "ARE BRATS":**

Annoying
 Resentful
 Easily annoyed
 Blames others
 Rule breaker
 Argues with adults
 Temper
 Spiteful/vindictive

**Conduct Disorder Diagnosis****TRAP**

Theft – breaking and entering, deceiving, non-confrontational stealing
 Rule breaking – running away, skipping school, out late
 Aggression – people, animals, weapons, forced sex
 Property destruction

- see **Pediatrics:**
 - Child Abuse, P15
 - Chronic Recurrent Abdominal Pain, P42
 - Developmental Delay, P26
 - Elimination Disorders, P12
 - Learning Disability, P28
 - Intellectual Disability, P26
 - Sleep Disturbances, P13

Psychodynamic Therapies

- theory: one's present outlook is shaped by one's past and unconscious psychological forces
- insight allows change in personality and behaviour
- conflict – three stages
 - non-resolvable conflict
 - attempt to repress
 - return of conflict in disguised form (symptom or character trait)
- emphasis on early interaction with caregiver
- sources of information
 - past and present experiences and relationships
 - relationship with therapist
 - ♦ **transference:** unconscious re-enactment of early interpersonal patterns in relationship with therapist
 - ♦ **countertransference:** therapist's transference to patient
 - ♦ **resistance:** elements in the patient which oppose treatment
- techniques
 - free association: patient says whatever comes to mind
 - dream analysis
- stage of change important for all conflict resolutions

Defense Mechanisms

- defense mechanisms are unconsciously activated by the patient in response to anxiety provoking events and feelings

Table 13. Defense Mechanisms

Level 1: Psychotic Defenses

Common in psychosis; normally seen throughout childhood and in dreams

- **Denial:** replacing external reality with wishful fantasy
- **Distortion:** reshaping of reality to meet inner beliefs, resulting in unrealistic and overvalued ideas
- **Projection:** interpreting internal impulses as though they are outside self; in psychosis seen as frank delusion about reality (e.g. persecutory delusions)

Level 2: Immature Defenses

Common in personality disorders, severe depression. Normally seen throughout adolescence

- **Acting out:** express unconscious wish through impulsive action, rather than inhibit it
- **Blocking:** of thinking, affect, or impulse
- **Hypochondriasis:** exaggeration of illness in order to avoid anxiety-provoking situations
- **Introjection:** internalizing qualities of an object (i.e. victim identifying with aggressor)
- **Passive-aggressive behaviour:** express aggression through passivity and masochism
- **Regression:** returning to an earlier stage of development to avoid present stressors
- **Somatization:** unconscious expression of psychic pain/tension as physical symptoms

Level 3: Neurotic Defenses

Common in adults

- **Controlling:** managing events to reduce inner conflict
- **Displacement:** shifting emotional response to an object/idea resembling that which is anxiety provoking
- **Externalization:** attributing personal aspects (e.g. moods, attitudes, conflicts) to external world and objects
- **Inhibition:** limiting function to avoid anxiety producing internal conflicts
- **Intellectualization:** using intellectual processing to avoid experiencing affect
- **Isolation:** separating objects/ideas from their associated affect (which is repressed)
- **Rationalization:** using rational explanations to justify behaviours that are unacceptable
- **Dissociation:** temporary modification of sense of self to avoid emotional distress
- **Reaction formation:** transforming an unacceptable impulse into its opposite
- **Repression:** withholding or removing from consciousness an idea/feeling
- **Sexualization:** bestowing sexual importance to objects

Level 4: Mature Defenses

Common in emotionally healthy adults

- **Altruism:** constructive service to others to experience empathy
- **Anticipation:** planning for future discomfort
- **Asceticism:** denying pleasurable effects of an experience (i.e. gratification from renunciation)
- **Humour:** overt expression of feelings in a comic fashion
- **Suppression:** postpone attention to impulse or conflict

The Role of the Therapeutic Alliance in Psychotherapy and Pharmacotherapy Outcome: Findings in the National Institute of Mental Health Treatment of Depression Collaborative Research Program

J Consult Clin Psychol 1996; 64(3):532-9

Study: Randomized clinical trial.

Participants: 255 male and female adults fulfilling research criteria for major depressive episode and who completed follow-up (total of 619 sessions).

Intervention: Four treatment arms: cognitive-behavioural therapy, interpersonal therapy, imipramine plus clinical management and placebo plus clinical management.

Methods: Clinical raters scored videotapes of early, middle and late therapy session.

Outcomes: Patients' and clinicians' perspectives and depressive symptomatology.

Results: Therapeutic alliance was found to have a significant effect on outcome in all treatment arms. Patient contribution to alliance had a significant effect on outcomes, whereas therapist contribution to alliance had no significant effect.

Conclusions: Therapeutic alliance is a common factor which significantly influences outcome.

Varieties of Psychodynamic Therapy

- **psychoanalysis** (exploratory psychotherapy)
 - original therapy developed by Freud, goal is self-revelation and insight
 - the exploration of the meaning of early experiences and how they affect emotions and patterns of behaviour presently
 - time intensive (e.g. 4-5 times/week for 3-7 years)
 - for individuals who can tolerate ambiguity in explorations of feelings and treatment
- **supportive psychotherapy**
 - goal is not insight but reduction of anxiety
 - strengthen healthy defense mechanisms to assist day-to-day functioning
 - techniques include: enhancing self-esteem, clarification, confrontation, rationalization, reframing, encouragement, rehearsal/anticipation, de-catastrophizing, allowing “venting” of frustrations
- **short term/brief psychotherapy**
 - resolution of particular emotional problems, or acute crisis
 - number of sessions agreed on at outset (6-20)
- **interpersonal psychotherapy**
 - short-term treatment looking at relationship patterns and teaching coping mechanisms
 - focus on personal social roles and relationships to help deal with problems in current functioning

Behaviour Therapy

- modification of internal or external events which precipitate or maintain emotional distress; useful in the treatment of anxiety disorders, substance abuse, paraphilias
- **systematic desensitization**: mastering anxiety-provoking situations by approaching them gradually and in a relaxed state that limits anxiety
- **flooding**: confronting feared stimulus for prolonged periods until it is no longer frightening
- **positive reinforcement**: strengthening behaviour and causing it to occur more frequently by rewarding it
- **negative reinforcement**: causing behaviour to occur more frequently by removing a noxious stimulus when desired behaviour occurs
- **extinction**: causing a behaviour to diminish by not rewarding it
- **punishment** (aversion therapy): causing a behaviour to diminish by applying a noxious stimulus

Cognitive Therapy

- theory: moods and feelings are influenced by one's thoughts
- psychiatric disturbances are frequently caused by habitual errors in thinking
- goal is to help patient become aware of automatic thoughts and correct assumptions with a more balanced view
- useful for depression, anxiety disorders, self-esteem problems
- use of this therapy presupposes a significant level of functioning
- patients asked to keep thought journal (often in chart form, with column headings “situation”, “feeling”, “thought” and “cognitive distortion”) to monitor their thoughts, when/where they think these thoughts, how the thoughts make them feel and what their underlying error in thinking might be

Cognitive Behaviour Therapy

- combines cognitive and behaviour therapies to teach the patient to weaken connections between thinking patterns, habitual behaviours and mood/anxiety problems
- good for treatment of mild/moderate depression/anxiety

Other Therapies

- **group psychotherapy**
 - goals: self-understanding, acceptance, social skills
 - creates a microcosm of society
- **family therapy**
 - family system considered more influential than individual
 - structural focus
 - ◆ here and now
 - ◆ re-establish parental authority
 - ◆ strengthen normal boundaries
 - ◆ re-arrange alliances
- **hypnosis**: mixed evidence for the treatment of pain, phobias, anxiety, and smoking cessation
- **dialectical behaviour therapy**: a form of CBT originally developed for borderline patients but since found to be effective for the treatment of several other disorders; focuses on four types of skills: mindfulness, emotion regulation, interpersonal effectiveness, and distress tolerance; individual and group therapy settings
- **mindfulness-based cognitive therapy**: derived from Buddhist meditative practices; aims to help people attend to thoughts, behaviours and emotions non-judgmentally and in the moment using guided breathing exercises

Two-year Randomized Controlled Trial and Follow-up of Dialectical Behaviour Therapy vs. Therapy by Experts for Suicidal Behaviours and Borderline Personality Disorder

Arch Gen Psychiatry 2006; 63(7):757-66

Objective: To determine how DBT compares with non-behavioural psychotherapy.

Study: One-year randomized controlled trial followed by one year follow-up period.

Patients: 100 women with recent suicidal and self-injurious behaviours meeting DSM criteria and matched to various demographic data.

Intervention: One year of DBT or one year of non-behavioural therapy.

Outcomes: Trimester assessments of suicidal behaviour, emergency services use, general psychological well-being.

Results: Patients receiving DBT were half as likely to attempt suicide, required less hospitalization for suicidal ideation, had lower medical risk for suicide attempts, were less likely to drop out of therapy and had fewer emergency room visits for suicidal ideation.

Conclusions: DBT is effective in reducing suicidal behaviour in patients with borderline personality disorder.

Pharmacotherapy

Antipsychotics

- “antipsychotics” and “neuroleptics” are terms used interchangeably
- **indications:** schizophrenia and other psychotic disorders, mood disorders with or without psychosis, violent behaviour, autism, Tourette's, somatoform disorders, dementia, OCD
- **onset:** immediate calming effect and decrease in agitation; thought disorder responds in 2-4 weeks

Table 14. Pathophysiology of Schizophrenia vs. Mechanism of Action of Antipsychotics

Brain Area	Pathophysiology in Schizophrenia	Typical Antipsychotic	Atypical Antipsychotic
Limbic System	Excess DA +ve symptoms (hallucinations, delusions)	D2 blockade Treats +ve symptoms	Weak 5-HT block, D2/1 blockade maintained Treats +ve symptoms
Frontal Cortex	Decreased DA -ve symptoms (flat affect, anhedonia, avolition), cognitive impairment	D2 blockade May worsen -ve symptoms and cognitive impairment	Robust 5-HT block increases DA transmission Theoretical improvement in negative/cognitive symptoms only observed with clozapine
Basal Ganglia	Unchanged	D2 blockade Relative ACh excess causes EPS symptoms	Robust 5-HT block increases DA transmission Decreased EPS incidence
Tuberoinfundibular Tract	Unchanged	D2 blockade Hyperprolactinemia	5-HT block increases DA Less hyperprolactinemia

DA = dopamine; 5-HT = serotonin; ACh = acetylcholine; EPS = extrapyramidal symptoms

Note: specific “typical” and “atypical” antipsychotics vary in terms of binding to adrenergic, 5-HT, cholinergic and histaminergic sites leading to different side effect profiles

Rational Use of Antipsychotics

- no reason to combine antipsychotics
- choosing an antipsychotic
 - all antipsychotics are equally effective
 - atypical antipsychotics are as effective as typical antipsychotics but have better side effect profiles
 - choose a drug patient has responded to in the past or that was used successfully in a family member
- route: PO; short-acting or long-acting depot IM injections; sublingual
- minimum 6 months, usually for life

Table 15. Common Antipsychotic Agents

	Starting Dose	Maintenance	Maximum	Relative Potency (mg)
Typicals (In order of potency from high to low)				
Pimozide (Orap®)	0.5-1 mg PO bid	2-12 mg/d PO	20 mg/d PO	1
Haloperidol (Haldol®)	2-5 mg IM q4-8h 0.5-5 mg PO b/tid 0.2 mg/kg/d PO	Based on clinical effect	20 mg/d PO	2
Fluphenazine enanthate (Moditen®, Modecate® for IM formulation)	2.5-10 mg/d PO	1-5 mg PO qhs 25 mg IM/SC q1-3 weeks	20 mg/d PO	2
Zuclopenthixol HCl (Clopixol®)	20-30 mg/d PO	20-40 mg/d PO	100 mg/d PO	4
Zuclopenthixol acetate (Acuphase®)	50-150 mg IM q48-72h		400 mg IM (q2 weeks)	
Zuclopenthixol decanoate (Cloxipol Depot®)	100 mg IM q1-4 weeks	150-300 mg IM q2 weeks	600 mg IM/week	
Trifluoperazine (Stelazine®)	2-5 mg PO bid	2-15 mg PO bid	60 mg/d PO	5
Perphenazine (Trilafon®)	8-16 mg PO b/tid	4-8 mg PO t/qid	64 mg/d PO	10
Loxapine HCl (Loxitane®)	10 mg PO tid 12.5-50 mg IM q4-6h	60-100 mg/d PO	250 mg/d PO	10
Thioridazine (Mellaril®)	25-100 mg PO tid	100-400 mg PO bid	800 mg/d PO	100
Chlorpromazine (Largactil®)	10-15 mg PO b/t/qid	400 mg/d PO	1000 mg/d PO	100
Atypicals				
Risperidone (Risperdal®, Risperdal Consta® for IM long acting preparation)	1-2 mg OD/bid	4-8 mg/d PO 25 mg IM q2 weeks	8 mg/d PO	High potency
Olanzapine (Zyprexa®, Zydys®)	5 mg/d PO	10-20 mg/d PO	30 mg/d PO	↓ Low potency
Ziprasidone (Zeldox®)	40 mg/d IM	80-160 mg/d IM	160 mg/d IM	
Clozapine (Clozaril®)	25 mg PO bid	300-600 mg/d PO	900 mg/d PO	
Quetiapine (Seroquel®)	25 mg PO bid	400-800 mg/d PO	800 mg/d PO	
Aripiprazole (Ablify®)	10-15 mg/d PO	10-15 mg/d PO	30 mg/d PO	

Side Effects of Typical Antipsychotics

- low potency: anticholinergic, antiadrenergic, anti-histaminic side effects
- high potency: risk of movement disorder side effects (extrapyramidal side effects) and neuroleptic malignant syndrome (allergic reaction)

Table 16. Commonly Used Atypical Antipsychotics

	Risperidone (Risperdal®)	Olanzapine (Zyprexa®, Zydys®)	Quetiapine (Seroquel®)	Clozapine (Clozaril®)	Ziprasidone (Zeldox®)
Mechanism	Blocks 5-HT ₂ , D2 and adrenergic receptors	Blocks 5-HT _{2,3,6} , D1-D4, muscarinic, adrenergic, histaminergic receptors	Blocks 5-HT _{2A} , D1-2, adrenergic and histaminergic receptors	Blocks 5-HT _{2,3} , D1-4, muscarinic, histaminergic receptors	Blocks 5-HT _{2A} , and moderate D2 receptor antagonism; moderately potent adrenergic and histaminergic blocker
Advantages	Low incidence of EPS at lower doses (<8 mg)	Better overall efficacy compared to haloperidol Well tolerated Low incidence of EPS and TD	Associated with less weight gain compared to clozapine and olanzapine	Most effective for treatment-resistant schizophrenia Does not worsen tardive symptoms; may treat them Approximately 50% of patients benefit, especially paranoid patients and those with onset after 20 years	
Disadvantages	SE: insomnia, agitation, EPS , H/A, anxiety, prolactin, postural hypotension, constipation, dizziness, weight gain	SE: mild sedation, insomnia, dizziness, minimal anticholinergic, early AST and ALT elevation, restlessness Weight gain associated with increased risk of diabetes mellitus and hyperlipidemia	SE: H/A, sedation, dizziness, constipation Most sedating of first line atypicals	SE: drowsiness/sedation, hypersalivation, tachycardia, dizziness, EPS, NMS 1% agranulocytosis	SE: sedation, nausea, constipation, dyspepsia
Comments	Quick dissolve (M-tabs), and long-acting (Consta®) formulations available	Quick dissolve formulation (Zydys®) used commonly in ER setting for better compliance IM form available		Weekly blood counts for at least 1 month, then q2weeks Do not use with drugs which may cause bone marrow suppression due to risk of agranulocytosis	

Note: Risk of weight gain: Clozapine/Olanzapine > Risperidone/Quetiapine > Ziprasidone

Atypical Antipsychotics

- fewer EPS than typicals (except risperidone above 8 mg/d)
- risperidone, olanzapine, quetiapine are the “first line atypical antipsychotics”
- no significant difference in efficacy, speed of response and stability of remission between first line atypicals
- disadvantage: expensive, metabolic side effects

Long-Acting Preparations

- antipsychotics formulated in oil for deep IM injection (see Table 15)
- received on an outpatient basis
- indications: individuals with schizophrenia or other chronic psychoses who relapse because of non-adherence
- dosing: start at low dosages, and then titrate every 2 to 4 weeks to maximize safety and minimize side effects
- should be exposed to oral form prior to first injection
- side effects: risk of EPS, parkinsonism, increased risk of neuroleptic malignant syndrome

Canadian Guidelines for the Treatment of Acute Psychosis in the Emergency Setting

- haloperidol 5 mg IM ± 2 mg IM lorazepam
- olanzapine 2.5-10 mg (PO, IM, quick dissolve)
- risperidone 2 mg (M-tab, liquid)

Table 17. Side Effects of Antipsychotics

System	Side Effects
Anticholinergic	Dry mouth, difficulty urinating, constipation, blurred vision, toxic-confusional states
Alpha-adrenergic blockade	Orthostatic hypotension, impotence, failure to ejaculate
Dopaminergic blockade	Extrapyramidal syndromes (dystonia, akathisia, pseudo-Parkinsonism, dyskinesia), galactorrhea, amenorrhea, impotence, weight gain
Anti-histamine	Sedation
Hematologic	Agranulocytosis (clozapine)
Hypersensitivity reactions	Liver dysfunction Blood dyscrasias Skin rashes Neuroleptic malignant syndrome Altered temperature regulation (hypothermia or hyperthermia)
Endocrine	Metabolic syndrome (see side bar)



Commonly Used Atypical Antipsychotics

ROCS

Risperidone
Olanzapine
Clozapine
Seroquel (quetiapine)



Anticholinergic Effects

Red as a beet
Hot as a hare
Dry as a bone
Blind as a bat
Mad as a hatter



Metabolic Syndrome

Atypical antipsychotics have been linked to weight gain, hyperglycemia, and lipid abnormalities and are associated with an increased risk of metabolic syndrome (a collection of clinical and laboratory abnormalities including abdominal obesity, insulin resistance, hypertension, low levels of high-density lipoprotein cholesterol, and high levels of triglycerides).



Features of Neuroleptic Malignant Syndrome

FARM

Fever

Autonomic changes (e.g. increased HR/BP, sweating)

Rigidity of muscles

Mental status changes (e.g. confusion)

FARM symptoms are also seen in

Serotonin Syndrome (SS).

SS can be distinguished from NMS by the following:

SS	NMS
Twitchy, shivering, restless	Severe global rigidity
Flushed, sweaty	Pallor
Vomiting, diarrhea, abdominal pain	No GI symptoms

Neuroleptic Malignant Syndrome (NMS)

- **psychiatric emergency**
- due to massive dopamine blockade; increased incidence with high potency and depot neuroleptics
- **risk factors**
 - medication factors
 - ♦ sudden increase in dosage, or starting a new drug
 - patient factors
 - ♦ medical illness
 - ♦ dehydration
 - ♦ exhaustion
 - ♦ poor nutrition
 - ♦ external heat load
 - ♦ sex: male
 - ♦ age: young adults
- **clinical presentation**
 - fever, autonomic reactivity, rigidity, mental status changes (usually occur first)
 - develops over 24-72 hours
 - labs: increased CPK, leukocytosis, myoglobinuria
- **treatment:** discontinue drug, hydration, cooling blankets, dantrolene (hydrantoin derivative, used as a muscle relaxant), bromocriptine (DA agonist)
- **mortality:** 5%

Extrapyramidal Symptoms (EPS)

- incidence related to increased dose and potency
- acute (early-onset; reversible) vs. tardive (late-onset; often irreversible)

Table 18. Extrapyramidal Symptoms

	Dystonia	Akathisia	Pseudoparkinsonism	Dyskinesia
Acute or Tardive	Both	Both	Acute	Tardive
Risk Group	Acute: Young Asian and Black males		Elderly females	Elderly females
Presentation	Sustained abnormal posture; torsions, twisting, contraction of muscle groups; muscle spasms (e.g. oculogyric crisis, laryngospasm, torticollis)	Motor restlessness; Crawling sensation in legs relieved by walking; very distressing, increased risk of suicide and poor adherence	Tremor Rigidity (cogwheeling) Akinesia Postural instability (decreased/absent arm-swing, stooped posture, shuffling gait, difficulty pivoting)	Purposeless, constant movements, involving facial and mouth musculature , or less commonly, the limbs
Onset	Acute: within 5 d Tardive: >90 d	Acute: within 10 d Tardive: >90 d	Acute: within 30 d	Tardive: >90 d
Treatment	Acute: benztropine or diphenhydramine	Acute: lorazepam, propranolol or diphenhydramine; reduce or change neuroleptic to lower potency	Acute: benztropine (or benzodiazepine if side effects); reduce or change neuroleptic to lower potency	Tardive: no good treatment; may try clozapine; discontinue drug or reduce dose



Tardive Dyskinesia may include grimacing, tongue protrusion, lip smacking, and rapid eye movement.

Antiparkinsonian Agents (Anticholinergic Agents)

- types
 - benztropine (Cogentin®) 2 mg PO, IM or IV OD (~1-6 mg)
 - amantadine (Symmetrel®) 100 mg PO bid (100-400 mg)
 - diphenhydramine (Benadryl®) 25-50 mg PO/IM qid
- do not always prescribe with neuroleptics
 - give only if at high risk for acute EPS or if acute EPS develops
- do not give these for tardive syndromes because they worsen the condition

Antidepressants

- onset of effect
 - neurovegetative symptoms – 1-3 weeks
 - emotional/cognitive symptoms – 2-6 weeks
- may use mild stimulant (e.g. methylphenidate) for severe neurovegetative symptoms briefly and taper down as antidepressant effect increases
- taper TCAs slowly (over weeks-months) because they can cause withdrawal reactions
- tapering of any kind of antidepressant may be required based on the half-life of the medication and the patient's individual sensitivity
- it is important to be particularly vigilant over the first 2 weeks of therapy as neurovegetative symptoms may start to resolve while emotional and cognitive symptoms may not (patients may be particularly at risk for suicidal behaviour during this time)
- treatment of bipolar depression: monotherapy with antidepressants is not advisable as a switch from depression to mania can occur. If the patient is medication-naïve, initiate therapy with a mood stabilizer plus an SSRI or bupropion. For patients taking mood stabilizers, consider adding or switching to lithium or lamotrigine, or adding an SSRI or bupropion

Table 19. Common Antidepressants

Class	Drug	Daily Starting Dose (mg)	Therapeutic Dose (mg)
SSRI	fluoxetine (Prozac®)	20	20-80
	fluvoxamine (Luvox®)	50-100	150-300
	paroxetine (Paxil®)	10	20-60
	sertraline (Zoloft®)	50	50-200
	citalopram (Celexa®)	20	20-60
	escitalopram (Cipralex®)	10	10-20
SNRI	venlafaxine (Effexor®)	37.5-75	75-225
	duloxetine (Cymbalta®)	40	40-60
NDRI	bupropion (Wellbutrin®)	100	300-450
TCA (3° Amines)	amitriptyline (Elavil®)	75-100	150-300
	imipramine (Tofranil®)	75-100	150-300
TCA (2° Amines)	nortriptyline (Aventyl®)	75-100	75-150
	desipramine (Norpramin®)	100-200	150-300
MAOI	phenelzine (Nardil®)	45	60-90
	tranylcypromine (Parnate®)	30	10-60
RIMA	moclobemide (Manerix®)	300	300-600
NASSA	mirtazapine (Remeron®)	15	15-45

(SSRI=selective serotonin reuptake inhibitors; SNRI=serotonin and norepinephrine reuptake inhibitors; NDRI=norepinephrine and dopamine reuptake inhibitors; TCA=tricyclic antidepressants; MAOI= monoamine oxidase inhibitors; RIMA=reversible inhibition of MAO-A; NASSA=noradrenergic and specific serotonin antagonists)

Treatment Strategies for Refractory Depression (see Figure 2)

- optimization:** ensuring adequate drug doses for the individual
- augmentation:** the addition of a medication that is not considered an antidepressant to an antidepressant regimen (e.g. thyroid hormone, lithium, atypical antipsychotics)
- combination:** the addition of another antidepressant to an existing treatment regimen (e.g. the addition of bupropion to an SSRI or SNRI)
- substitute:** change in the primary antidepressant (within or outside a class) Note: it is important to fully treat the symptoms of depression in order to decrease rates and severity of relapses

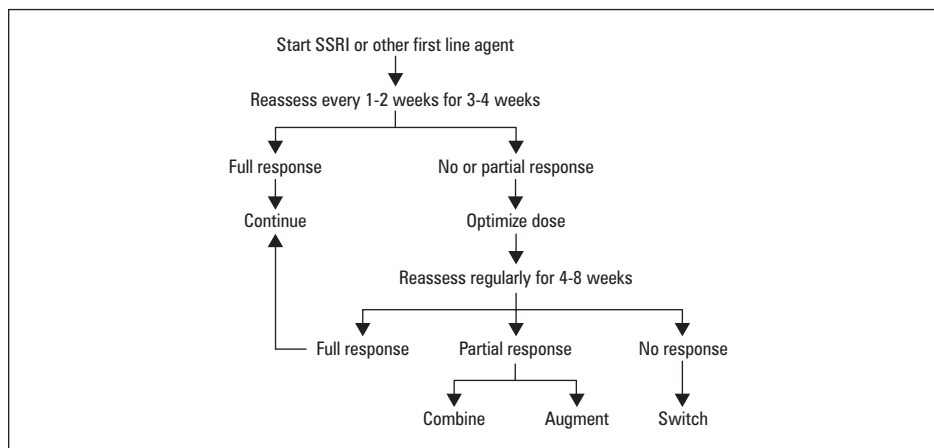


Figure 2. Treatment of Depression

Selective Serotonin Reuptake Inhibitors (SSRIs) versus Other Antidepressants for Depression (Cochrane Review)

Cochrane Database of Systematic Reviews 2004; Issue 3

This systematic review of 98 RCTs compared the efficacy of SSRIs with other kinds of antidepressants in the treatment of patients with depressive disorders.

Conclusions: There is no significant difference in the effectiveness of SSRIs versus TCAs. Consider relative patient acceptability, toxicity and cost when choosing.



Tips On Choosing Antidepressants

- All SSRIs have similar effectiveness, but consider side effect profiles and half-lives.
- Bupropion causes less sexual dysfunction, weight gain, and sedation but is contraindicated for patients with history of seizure, stroke, brain tumour, brain surgery or closed head injury. Also used to treat eating disorders. Not recommended for anxiety because of stimulating effects.
- Mirtazapine useful if insomnia or agitation are prominent, or to treat depression with cachexia.
- Trazodone mainly used as adjunct for SSRI-induced sleep disturbances.
- Sertraline, citalopram, and escitalopram have the least interactions with other drugs and are sleep-wake neutral.
- Fluoxetine and paroxetine are the most activating drugs and should be taken in the morning.
- Fluvoxamine is always sedating and should be taken in the evening.



How Long to Treat?

6-12 months: if first or second episode
2 years: if third episode, elderly, psychotic features, refractory depression, >2 episodes in 5 years



Psychopharmacology of SSRIs

Post-Synaptic Serotonin Receptor Stimulated	Effect/Side Effect
5HT1A centrally	• Relief of depression • Anxiolytic effect
5HT2A in spinal cord	• Sexual dysfunction: delayed ejaculation, anorgasmia, decreased interest/libido • Rx with bupropion
5HT2C/5HT2A in brain	• Activation: anxiety, insomnia • Worst with fluoxetine, paroxetine • Warn patients anxiety may worsen in first 1-2 weeks of treatment
5HT3A in gut	• GI upset: nausea, vomiting, bloating • Take with food

Table 20. Commonly Used Antidepressants

	TCA	SSRI	MAOI	SNRI
Considerations	OCD (clomipramine) Melancholic depression	Anxiety states, OCD, eating disorders, seasonal depression, typical and atypical depression	For moderate/severe depression that does not respond to SSRI Atypical depression	Depression, anxiety disorders
Mode of Action	Block norepinephrine and serotonin reuptake	Block serotonin reuptake only	Irreversible inhibition of monoamine oxidase A and B Leads to ↑ norepinephrine and serotonin	Block norepinephrine and serotonin reuptake
Side Effects	<i>Anticholinergic effects:</i> (see Table 17) <i>Noradrenergic effects:</i> tremors, tachycardia, sweating, insomnia, erectile and ejaculation problems <i>α-1 adrenergic effects:</i> orthostatic hypotension <i>Antihistamine effects:</i> sedation, weight gain <i>CNS:</i> sedation, stimulation, ↓ seizure threshold <i>CVS:</i> ↑ HR, conduction delay	Fewer than TCA, therefore increased compliance <i>CNS:</i> restlessness, tremor, insomnia, headache, drowsiness <i>GI:</i> N/V, diarrhea, abdominal cramps, weight loss <i>Sexual dysfunction:</i> impotence, anorgasmia <i>CVS:</i> increased HR, conduction delay Serotonin syndrome, EPS, SIADH	Hypertensive crises with tyramine rich foods (e.g. wine, cheese) develop headache, flushes, palpitations, N/V, photophobia Dizziness, reflex tachycardia, postural hypotension, sedation, insomnia Weight gain Social dysfunction Energizing Minimal anticholinergic and antihistamine effects	Low dose side effects include insomnia (serotonergic) Higher dose side effects include: tremors, tachycardia, sweating, insomnia, dose-dependent increase in diastolic BP (noradrenergic)
Risk in Overdose	Toxic in OD 3 times therapeutic dose is lethal <i>Presentation:</i> anticholinergic effects, CNS stimulation, then depression and seizures <i>ECG:</i> ↑ QT (duration reflects severity) <i>Treatment:</i> activated charcoal, cathartics, supportive treatment, IV diazepam for seizure, physostigmine salicylate for coma Do not give ipecac, as can cause rapid neurologic deterioration and seizures	Relatively safe in OD	Toxic in OD, but wider margin of safety than TCA	Tachycardia and N/V seen in acute overdose
Drug Interactions	MAOI, SSRI EtOH	SSRIs inhibit P450 enzymes; therefore will ↑ levels of drugs metabolized by P450 system	EtOH Hypertensive crises with noradrenergic medications (e.g. TCA, decongestants, amphetamines) Serotonin syndrome with serotonergic drugs (e.g. SSRI, tryptophan, dextromethorphan)	MAOI, SSRI Does not seem to inhibit P450 system
	NDRI	RIMA	NASSA	
Considerations	Depression, seasonal depression	Depression unresponsive to other therapies	Useful in patients with insomnia, agitation or depression with cachexia	
Mode of Action	Block norepinephrine and dopamine reuptake	Reversible inhibitor of monoamine oxidase A Leads to ↑ norepinephrine and serotonin	Enhance central noradrenergic and serotonergic activity by inhibiting presynaptic α-2 adrenergic receptors	
Side Effects	<i>CNS:</i> dizziness, headache, tremor, insomnia <i>CVS:</i> dysrhythmia, hypertension <i>GI:</i> dry mouth, N/V, constipation, ↑ appetite <i>Other:</i> agitation, anxiety, anaphylactoid reaction	<i>CNS:</i> dizziness, headache, tremor, insomnia <i>CVS:</i> dysrhythmia, hypotension <i>GI:</i> dry mouth, N/V, diarrhea, abdominal pain, dyspepsia <i>GU:</i> delayed ejaculation <i>Other:</i> diaphoresis	<i>CNS:</i> somnolence, dizziness, seizure (rare) <i>Endocrine:</i> ↑ cholesterol, ↑ triglycerides <i>GI:</i> Constipation, ↑ ALT	
Risk in Overdose	Tremors and seizures seen in acute overdose	Risk of fatal overdose when combined with citalopram or clomipramine	Mild symptoms with overdose	
Drug Interactions	MAOI Drugs that reduce seizure threshold: antipsychotics, systemic steroids, quinolone antibiotics, antimalarial drugs	MAOI, SSRI, TCA Narcotics	MAOI, SSRI, SNRI, RIMA	

Serotonin Syndrome

- thought to be due to over-stimulation of the serotonergic system
- can result from medication combinations such as SSRI+MAOI, SSRI+tryptophan, MAOI+meperidine, MAOI+tryptophan
- **rare but potentially life-threatening adverse reaction to SSRIs**, especially when switching from an SSRI to an MAOI
- symptoms include nausea, diarrhea, palpitations, chills, restlessness, confusion, and lethargy but can progress to myoclonus, hyperthermia, rigor and hypertonicity
- treatment: discontinue medication and administer emergency medical care as needed
- important to distinguish from NMS (see side box, PS44)

Discontinuation Syndrome

- caused by the abrupt cessation of an antidepressant
- observed most frequently with paroxetine, fluvoxamine, and venlafaxine
- symptoms usually begin within 1-3 days, and include: anxiety, insomnia, irritability, mood lability, N/V, dizziness, headache, dystonia, tremor, chills, fatigue, lethargy and myalgia
- treatment: symptoms may last between 1-3 weeks, but can be relieved within 24 hours by restarting antidepressant therapy at the same dose the patient was taking, and initiating a slow taper over several weeks
- consider drug with longer half-life such as fluoxetine

Mood Stabilizers

First-Line

Lithium/Valproic Acid (\pm antipsychotic)

- before initiating, get baseline: CBC, ECG (if patient >45 years old or cardiovascular risk), urinalysis, BUN, Cr, electrolytes, TSH
- before initiating lithium: screen for pregnancy, thyroid disease, seizure disorder, neurological, renal, cardiovascular diseases
- may need acute coverage with benzodiazepines or antipsychotics
- use carbamazepine in non-responders and rapid cycling
- can combine lithium and carbamazepine or valproic acid safely in lithium non-responders
- olanzapine may be used as a mood stabilizer, in conjunction with other mood stabilizers
- lithium and lamotrigine have established antidepressant efficacy

Lithium Toxicity (see Table 21)

- clinical diagnosis, as toxicity can occur at therapeutic levels
- **common causes**
 - overdose
 - sodium or fluid loss
 - concurrent medical illness
- **clinical presentation**
 - GI: severe nausea/vomiting and diarrhea
 - cerebellar: ataxia, slurred speech, lack of coordination
 - cerebral: drowsiness, myoclonus, choreiform or Parkinsonian movements, upper motor neuron signs, seizures, delirium, coma
- **management**
 - discontinue lithium for several doses and begin again at a lower dose when lithium level has fallen to a nontoxic range
 - serum lithium levels, BUN, electrolytes
 - saline infusion
 - hemodialysis if lithium >2 mmol/L, coma, shock, severe dehydration, failure to respond to treatment after 24 hours, or deterioration

Second-Line/Adjuvant Mood Stabilizers

Lamotrigine (Lamictal®)

- **indications:** treatment of dysphoric mania, mixed episodes and rapid cycling BAD, bipolar type 1 depression, prevention of mania and depression
- **mechanism:** may inhibit 5-HT₃ receptors and potentiate DA activity
- **side effects**
 - CNS: dizziness, headache, ataxia, nausea, somnolence, fever, anxiety
 - skin: rash, Stevens-Johnson syndrome (0.1%)



Symptoms of Antidepressant Discontinuation

FINISH

Flu-like symptoms
Insomnia
Nausea
Imbalance
Sensory disturbances
Hyperarousal (anxiety/agitation)

Sequenced Treatment Alternatives to Relieve Depression

Journal of Psychosocial Nursing 2008; 46:21-24
Study: Prospective randomized anti-depressant treatment trial.

Patients: 4000 patients with major depressive disorder.

Objective: To compare the efficacy and tolerability of various antidepressant therapies through four sequential treatment levels.

Intervention: Level 1-citalopram → if relapse → Level 2-citalopram + bupropion SR, sertraline, venlafaxine XR, or cognitive psychotherapy. Level 2A-switch to bupropion or venlafaxine XR. Level 3-either mirtazapine or nortriptyline + lithium, T3. Level 4-tranylcypromine or venlafaxine XR + mirtazapine.

Results: Remission rates were 28% for Level 1, 17% for Level 2, 12-25% for Level 3, and 7-14% for Level 4. When more treatment steps are required, lower remission rates, greater degrees of tolerance, and higher rates of relapse.



Long term lithium use can lead to a nephropathy and diabetes insipidus in some patients.



Lithium Side Effects

LITHIUM

Leukocytosis
Insipidus (diabetes)
Tremor, teratogenicity
Hypothyroidism
Increased weight
"V" omitting, nausea
Miscellaneous (e.g. ECG changes, acne)

Table 21. Commonly Used Mood Stabilizers

	Lithium	Lamotrigine (Lamictal®)	Divalproex (Epival®)	Carbamazepine (Tegretol®)
Indications	Maintenance therapy of bipolar disorder Treatment of acute mania Augmentation of antidepressants in MDE and OCD Schizoaffective disorder Chronic aggression and antisocial behaviour Recurrent depression	Treatment of bipolar disorder Rapid cycling bipolar disorder Mixed phase/Dysphoric mania Prevention of mania and depression	Maintenance therapy of bipolar disorder Treatment of acute mania Rapid cycling bipolar disorder Mixed phase/Dysphoric mania	Maintenance therapy of bipolar disorder Treatment of acute mania Rapid cycling bipolar disorder
Mode of Action	Unknown Therapeutic response within 7-14 days	May inhibit 5-HT ₃ receptors May potentiate DA activity	Depresses synaptic transmission Raises seizure threshold	Depresses synaptic transmission Raises seizure threshold
Dosage	Adult: 600-1500 mg/day Geriatric: 150-600 mg/day Usually once/day dosing	Starting: 12.5-15 mg/day Maximum: 500 mg/day Dose adjusted in patients taking other anti-convulsants	750-2500 mg/day Usually tid dosing	400-1600 mg/day Usually bid or tid dosing
Therapeutic Level	Adult: 0.5-1.2 mmol/L (1.0-1.25 mmol/L for acute mania) Geriatric: 0.3-0.8 mmol/L	Therapeutic plasma level not established Dosing based on therapeutic response	17-50 mmol/L	350-700 µmol/L
Monitoring	Monitor serum levels until therapeutic (always wait 12 hours after dose) Then monitor biweekly or monthly until a steady state is reached, then q2 months Monitor thyroid function q6 months, creatinine q6 months, urinalysis q1 year	Monitor for suicidality, particularly when initiating treatment	LFTs weekly x 1 month, then monthly, due to risk of liver dysfunction Watch for signs of liver dysfunction: nausea, edema, malaise	Weekly blood counts for first month, due to risk of agranulocytosis Watch for signs of blood dyscrasias: fever, rash, sore throat, easy bruising
Side Effects	<i>GI</i> : N/V, diarrhea, stomach pain <i>GU</i> : polyuria, polydipsia, GN, renal failure, nephrogenic DI <i>CNS</i> : fine tremor, lethargy, fatigue, headache <i>Hematologic</i> : reversible leukocytosis <i>Other</i> : teratogenic (Ebstein's anomaly), weight gain, edema, psoriasis, hypothyroidism, hair thinning, muscle weakness, ECG changes	<i>GI</i> : N/V, diarrhea <i>CNS</i> : ataxia, dizziness, diplopia, headache, somnolence <i>Skin</i> : rash (should d/c drug because of risk of Stevens-Johnson syndrome) , increased lamotrigine levels = increased risk of rash <i>Other</i> : anxiety	<i>GI</i> : liver dysfunction, N/V, diarrhea <i>CNS</i> : ataxia, drowsiness, tremor, sedation, cognitive blurring <i>Other</i> : hair loss, weight gain, transient thrombocytopenia, neural tube defects when used in pregnancy	<i>GI</i> : N/V, diarrhea, hepatic toxicity (↑ AST, ↑ ALT, ↑ LDH) <i>CNS</i> : ataxia, dizziness, slurred speech, drowsiness, confusion, nystagmus, diplopia <i>Hematologic</i> : transient leukopenia (10%), agranulocytosis, aplastic anemia <i>Skin</i> : rash (5% risk; should d/c drug because of risk of Stevens-Johnson syndrome) <i>Other</i> : neural tube defects when used in pregnancy
Interactions	NSAIDs decrease clearance		OCP	OCP

Anxiolytics

- **indications**

- short term treatment of transient forms of anxiety disorders, insomnia, alcohol withdrawal (especially delirium tremens), barbiturate withdrawal, organic brain syndrome (agitation in dementia), EPS and akathisia due to antipsychotics, seizure disorders, musculoskeletal disorders

- **relative contraindications**

- major depression (except as an adjunct to other treatment), history of drug/alcohol abuse, pregnancy, breast feeding

- **mechanism of action**

- benzodiazepines: potentiate binding of GABA to its receptors; results in decreased neuronal activity
- buspirone: partial agonist of 5-HT type 1A receptors

Rational Use of Anxiolytics (see Table 22)

- anxiolytics mask or alleviate symptoms; they do not cure them

Benzodiazepines

- should be used for limited periods (weeks-months) to avoid dependence
- all benzodiazepines are sedating
- have similar efficacy, so choice depends on half-life, metabolites and route of administration, OD or BID
- taper slowly over weeks-months because they can cause withdrawal reactions
 - low dose withdrawal: tachycardia, hypertension, panic, insomnia, anxiety, impaired memory and concentration, perceptual disturbances
 - high dose withdrawal: hyperpyrexia, seizures, psychosis, death
- avoid alcohol because of potentiation of CNS depression; caution with drinking and use of machinery
- **side effects**
 - CNS: drowsiness, cognitive impairment, reduced motor coordination, memory impairment
 - physical dependence, tolerance develops
- **withdrawal**
 - symptoms: anxiety, insomnia, dysperceptions, autonomic hyperactivity (less common)
 - onset: 1-2 days (short-acting), 2-4 days (long-acting)
 - duration: weeks/months
 - complications: above 50 mg diazepam/day: seizures, delirium, arrhythmias, psychosis
 - management: taper with long-acting benzodiazepine
 - similar to, but less severe than alcohol withdrawal; can be fatal
- **overdose**
 - commonly used drug in overdose
 - ♦ overdose is rarely fatal
 - ♦ benzodiazepines are more dangerous and may cause death when combined with alcohol, other CNS depressants or TCAs

Benzodiazepine Antagonist – Flumazenil (Anexate®)

- use for suspected benzodiazepine overdose
- specific antagonist at the benzodiazepine receptor site

Buspirone (Buspar®)

- **primary use:** generalized anxiety disorder
- may be preferred over benzodiazepines because:
 - non-sedating
 - no interaction with alcohol
 - does not alter seizure threshold
 - not prone to abuse
- **onset of action:** 2 weeks
- **side effects:** dizziness, drowsiness, nausea, headache, nervousness, extrapyramidal

**Geriatric Benzodiazepines****LOT**

Lorazepam

Oxazepam

Temazepam

Also safe in liver disease because not metabolized by liver

**Benzos used for Alcohol Withdrawal**

Diazepam 20 mg PO/IV q1h prn

Lorazepam 2-5 mg PO/IV/SL for patients with liver disease, chronic lung disease, or elderly

Table 22. Common Anxiolytics

Class	Drug	Dose Range (mg/day)	t _{1/2} (hours)	Appropriate Use
Benzodiazepines				
Long-acting	clonazepam (Rivotril®)	0.25-4	18-50	Akathisia, generalized anxiety seizure prevention, panic disorder
	diazepam (Valium®)	2-40	30-100	Generalized anxiety, seizure prevention, muscle relaxant, alcohol withdrawal
	chlordiazepoxide (Librium®)	5-300	30-100	Sleep, anxiety, alcohol withdrawal
	flurazepam (Dalmane®)	15-30	50-160	Sleep
	alprazolam (Xanax®)	0.25-4.0	6-20	Panic disorder, high dependency rate
Short-acting	lorazepam (Ativan®)	0.5-6.0	10-20	Sleep, generalized anxiety, akathisia, alcohol withdrawal, sublingual available for very rapid action
	oxazepam (Serax®)	10-120	8-12	Sleep, generalized anxiety, alcohol withdrawal
	temazepam (Restoril®)	7.5-30	8-20	Sleep
	triazolam (Halcion®)	0.125-0.5	1.5-5	Shortest t _{1/2} , rapid sleep, but rebound insomnia
Azapirones	buspirone (Buspar®)	20-60	2-11	Generalized anxiety
	zopiclone (Imovane®)	5-7.5	3.8-6.5	Sleep

ECT in Society

Prior to the 1940's, ECT was performed without the use of muscle relaxants, resulting in seizures with full-scale convulsions and rare but serious complications such as vertebral and long-bone fractures. This practice may have led to negative societal perceptions of ECT, further perpetuated by barbaric depictions in popular culture. Despite ongoing stigmatization, ECT as it is practiced today is an effective and safe option for patients struggling with mental illness.

Efficacy of ECT in Depression: A Meta-Analytic Review*J of ECT* 2004; 20:13-20**Study:** Meta-analysis of randomized and non-randomized control trials.**Patients:** Individuals with unipolar and bipolar depression.**Methods:** MEDLINE search for relevant papers from 1966-2003.**Main Outcomes:** The Hamilton Depression Rating scale was used to determine response to treatment.**Results:** ECT was found to be superior to simulated ECT, placebo, TCAs, MAOIs, and anti-depressants in general.**Summary:** ECT is an efficacious treatment modality, particularly in severe and treatment-resistant depression.

Electroconvulsive Therapy

- induction of a grand mal seizure using an electrical pulse through the brain while the patient is under general anesthesia and a muscle relaxant
- unilateral vs. bilateral electrode placement
- **indications**
 - depression refractory to adequate pharmacological trial
 - high suicide risk
 - medical risk in addition to depression (dehydration, electrolytes, pregnancy)
 - previous good response to ECT
 - familial response to ECT
 - elderly
 - psychotic depression
 - catatonic features
 - marked vegetative features
 - acute schizophrenia
 - mania unresponsive to meds
- **side effects:** risk of anesthesia, memory loss (may be retrograde and/or anterograde, tends to resolve by 6 to 9 months, permanent impairment controversial), headaches, myalgias
- evidence that unilateral ECT causes less memory loss than bilateral but may not be as effective
- **contraindications:** increased intracranial pressure

Experimental Therapies

Deep Brain Stimulation (DBS)

- constant electrical stimulation of neuroanatomical targets that have been identified in the biological model of depression
- areas identified include the nucleus accumbens, internal capsule and subgenual cingulate cortex
- parameters such as active electrode location, pulse width, frequency and voltage may be manipulated

Transcranial Magnetic Stimulation (TMS)

- non-invasive magnetic stimulation of superficial neurons in the frontal cortex (main target: dorsolateral prefrontal cortex) hypothesized to normalize cortical activity in depressed patients
- meta-analyses show modest acute efficacy

Canadian Legal Issues



Common Forms

Table 23. Common Forms Under the Mental Health Act (in Ontario)

Form	Who Signs	When	Expiration Date	Right of Patient to Review Board Hearing	Options Before Form Expires
Form 1: Application by physician to hospitalize a patient for psychiatric assessment against his/her will to a schedule 1 facility (Form 42 given to patient)	Any MD	Within 7 days after examination	72 hours after hospitalization Void if not implemented within 7 days	No	Form 3 or Voluntary admission (Form 5) or Send home ± Follow-up
Form 2: Order for hospitalization and medical examination against his/her will by Justice of the Peace	Justice of the Peace	No statutory time restriction	7 days from when completed Purpose of form is complete once patient brought to hospital	No	Form 1 or Send home ± Follow-up
Form 3: Certificate of involuntary admission to a schedule 1 facility (Form 30 given to patient, notice to rights advisor)	Attending MD (different than MD who completed Form 1)	Before expiration of Form 1 Any time to change status of an informal patient	14 days	Yes (within 48 hours)	Form 4 or Form 5
Form 4: Certificate of renewal of involuntary admission to a schedule 1 facility (Form 30 given to patient, notice to rights advisor)	Attending MD following patient on Form 3	Prior to expiration of Form 3	First: 1 month Second: 2 months Third: 3 months (max)	Yes (within 48 hours)	Form 4 or Form 5
Form 5: Change to informal/voluntary status	Attending MD following patient on Form 3/4	Whenever deemed appropriate	N/A	N/A	N/A
Form 33: Notice to patient that patient is incompetent to consent to treatment of mental disorder and/or management of property	Attending MD	Whenever deemed appropriate	N/A	N/A	N/A



Form 1: A Primer

- Filled out when a patient is suspected of being an imminent harm to themselves (suicide) or others (homicide) or when they are incapable of self-care (e.g. not dressed for freezing weather) and are suffering from an apparent mental disorder.
- Based on any combination of the physician's own observations and facts communicated by others.
- Box A or Box B completed.
- Box A: Serious Harm Test**
 - The Past/Present Test assesses current behaviours/threats/attempts.
 - The Future Test assesses the likelihood of serious harm occurring as a result of the presenting mental disorder.
- Box B:** Patients with a known mental disorder, who are incapable of consenting to treatment (existing substitute decision-maker), have previously received treatment and improved, and are currently at risk of serious harm due to the same mental disorder.

Consent

- see Ethical, Legal and Organizational Aspects of Medicine, ELOAM2, ELOAM8

Community Treatment Order (CTO)

- known as "Brian's Law," Ontario passed legislature regarding CTOs on December 1, 2000
- similar CTOs have been implemented in Saskatchewan (1995), Manitoba (1997) and British Columbia (1999)
- purpose: to provide a person who suffers from a serious mental disorder with a comprehensive plan of community-based treatment and supervision that is less restrictive than being detained in a psychiatric facility
- intended for those who:
 - as a result of their serious mental disorder, experience a pattern of admission to a psychiatric facility where their condition is usually stabilized
 - after being released, these patients often lack supervision and stop treatment
 - due to the destabilization of their condition, these patients usually require re-admission to hospital

- criteria for a physician to issue a CTO
 - patient with a prior history of hospitalization
 - a community treatment plan for the person has been made
 - examination by a physician within the previous 72 hours before entering into the CTO plan
 - ability of the person subject to the CTO to comply with it
 - consultation with a rights adviser and consent of the person and the person's substitute decision maker, if any
- CTOs are valid for **six months** unless they are renewed or terminated at an earlier date
 - where the person fails to comply with the CTO
 - when the person or his/her substitute decision-maker withdraws consent to the community treatment plan
- CTO process is consent-based and all statutory protections governing informed consent apply
- the rights of a person subject to a CTO include:
 - the right to a review by the Consent and Capacity Board with appeal to the courts each time a CTO is issued or renewed
 - a mandatory review by the Consent and Capacity Board every second time a CTO is renewed
 - the right to request a re-examination by the issuing physician to determine if the CTO is still necessary for the person to live in the community
 - the right to review findings of incapacity to consent to treatment
 - provisions for rights advice

Duty to Inform/Warn

- see Ethical, Legal, and Organizational Aspects of Medicine, ELOAM5

References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, Text Revision. Washington, DC, American Psychiatric Publishing Inc., 2000.
- Ball JR, Mitchell PB, Corry JC, Skilecorn A, Smith M, Malhi GS. A randomized controlled trial of cognitive therapy for bipolar disorder: focus on long-term change. *J Clin Psychiatry*. 67(2): 277-86, 2006.
- Clinical Practice Guidelines: Treatment of Schizophrenia in Can J Psychiatry vol 50, suppl 1 Nov 2005, p19-28.
- Conley RR, Kelly DL. Pharmacologic Treatment of Schizophrenia. First Edition. Professional Communications Inc., U.S.A., 2000.
- DeRubeis RJ et al. Cognitive therapy vs. medications in the treatment of moderate to severe depression. *Arch Gen Psychiatry*. 62(4): 409-16, 2005.
- Ditto KE. SSRI discontinuation syndrome. Awareness as an approach to prevention. *Postgrad Med*. 2003 Aug;114(2):79-84.
- Folstein MF, Folstein SE and McHugh PR (1975). Mini-Mental State: A practical method for grading the state of patients for the clinician. *Journal of Psychiatric Research*. 12: 189-198.
- Gliatto MF, Rai AK. "Evaluation and Treatment of Patients With Suicidal Intention." *American Family Physician*, Volume 59, Number 6, 1999 pp. 1500-14.
- Hembree EA, Foa, EB. "Posttraumatic Stress Disorder: Psychological Factors and Psychosocial Interventions." *Journal of Clinical Psychiatry*, Volume 61, Supplement 7, 2000, pp. 33-9.
- Herrmann N. "Recommendations for the Management of Behavioural and Psychological Symptoms of Dementia." *Canadian Journal of Neurological Sciences*, Volume 28, Supplement 1, 2001, pp. S96-107.
- Howland RH. Sequenced Treatment Alternatives to Relieve Depression (STAR*D). Part 2: Study outcomes. *J Psychosoc Nurs Ment Health Serv*. 2008;46(10):21-4.
- Kahan, M, Wilson, L. Managing Alcohol, Tobacco and other Drug Problems: A pocket guide for physicians and nurses. Toronto, ON. Centre for Addiction and Mental Health. 2002.
- Kapur S, Zipursky RB, Remington G. "Clinical and Theoretical Implications of 5-HT₂ and D₂ Receptor Occupancy of Clozapine, Risperidone, and Olanzapine in Schizophrenia." *American Journal of Psychiatry*, Volume 156, Number 2, 1999, pp. 286-93.
- Koch, T. "A Tour of the Psychotropics." 4th ed. Mental Health Service-St-Michael's Hospital. Toronto, Canada.
- Krupnick JL et al. The role of the therapeutic alliance in psychotherapy and pharmacotherapy outcome: findings in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *J Consult Clin Psychol*. 64(3): 532-9, 1996.
- Linde K, Berner MM, Kriston L. St John's wort for major depression. *Cochrane Database of Systematic Reviews* 2008, Issue 4.
- Lineham MM et al. Two-year randomized controlled trial and follow-up of dialectical behaviour therapy vs. therapy by experts for suicidal behaviours and borderline personality disorder. *Arch Gen Psychiatry*. 63(7): 757-66, 2006.
- Long. P. www.mentalhealth.com. 2003.
- Lopez M, Torpac MG. "The Texas Children's Medication Algorithm Project: Report of the Texas Consensus Conference Panel on Medication Treatment of Childhood Attention-Deficit/Hyperactivity Disorder. Part I." *American Academy of Child and Adolescent Psychiatry*, Volume 39, Number 7, 2000, pp. 908-19.
- March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 2004;292(7):807-20.
- Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 2007;370(9584):319-28.
- MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. 1999;56(12):1073-86.
- National Institute on Drug Abuse Research Report Series, Methamphetamine Abuse and Addiction, NIH Publication Number 02-4210 reprinted January 2002.
- Noble. *Textbook of Primary Care Medicine*, p.466, 470. 3rd edition.
- Pagnin D, de Queiroz V, Pini S, Cassano GB. Efficacy of ECT in depression: a meta-analytic review. *J ECT* 2004;20(1):13-20.
- Patterson CJ, Gauthier S, Bergman H, Cohen C, Freightner JW, Feldman H, Hogan D. "Canadian Consensus Conference on Dementia: A Physician's Guide to Using the Recommendations." *CMAJ*, Volume 160, Number 12, 1999, pp. 1738-42.
- Perkins GD, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry* 2005;162(10):1785-804.
- Pliszka SR, Greenhill LL, Crismon ML, Sedillo A, Carlson C, Connors CK, McCracken JT, Swanson JM, Hughes CW, Liana ME.
- Rees L, Lipsedge M, Ball C, ed. (1997). *Textbook of Psychiatry*. London: Oxford University Press, P. 109.
- Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005;294(15):1934-43.
- Stahl SM. *Psychopharmacology of Antidepressants*. London: Martin Dunitz, 1998.
- Stahl SM. *Psychopharmacology of Antipsychotics*. London: Martin Dunitz, 1999.
- Szewczyk M. "Women's Health: Depression and Related Disorders." *Primary Care*, Volume 24, Number 1, 1997, pp. 83-101.
- Tasman. *Psychiatry* 1st ed. 1997. p.1208.
- Troiden, 1989, *Journal of Homosexuality*. 17: 253-267.
- Warneke L. "Breaking the urges of obsessive-compulsive disorder." *Canadian Journal of Diagnosis*, December 1996, h. page.
- Weller EB, Weller RA, Fristad MA. "Bipolar Disorder in Children: Misdiagnosis, Underdiagnosis, and Future Directions." *Journal of the American Academy of Child and Adolescent Psychiatry*, Volume 34, Number 6, 1995, pp. 709-714.
- Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004;363(9418):1341-5.
- Zimmerman, M. *Interview Guide for Evaluating DSM-IV Psychiatric Disorders and the Mental Status Examination*. East Greenwich, RI. Psych Products Press. 1994.

Helen Cheung, Yehoshua Gleicher and Lorraine Jensen, chapter editors

Doreen Ezeife and Nigel Tan, associate editors

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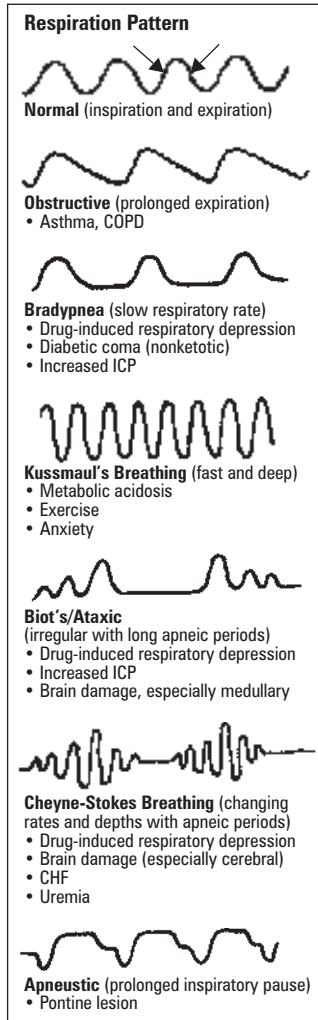


Figure 2. Respiration Patterns in Normal and Disease States

Approach to the Respiratory Patient

Basic Anatomy Review

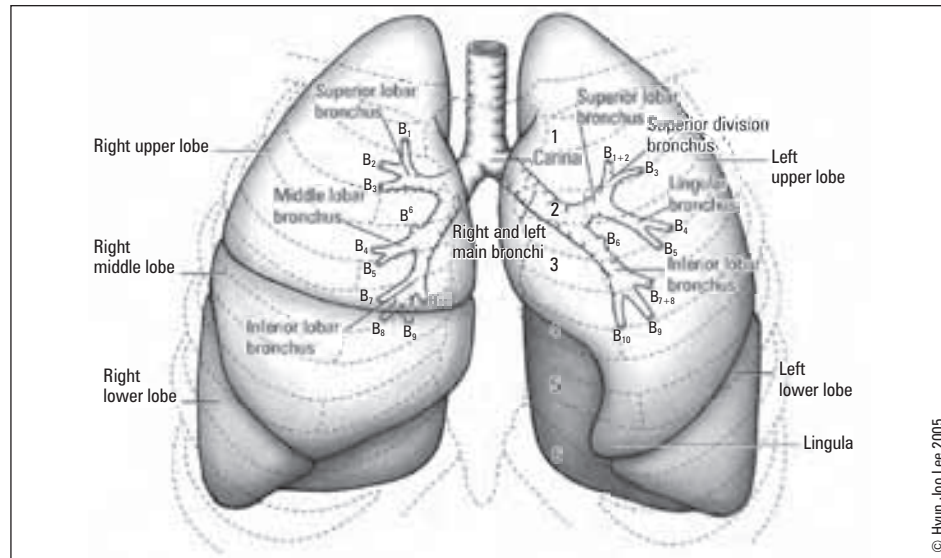


Figure 1. Lung Lobes and Bronchi

Differential Diagnoses of Common Presentations

Table 1. Differential Diagnosis of Dyspnea

Acute dyspnea (min-hrs)
Cardiac causes
Ischemic heart disease
CHF exacerbation
LVF with pulmonary edema
Cardiac tamponade
Pulmonary causes
Upper airway obstruction (anaphylaxis, foreign body)
Airway disease (asthma, COPD exacerbation, bronchitis)
Parenchymal lung disease (ARDS, pneumonia)
Pulmonary vascular disease (PE, vasculitis)
Pleural disease (pneumothorax, tension pneumothorax)
Respiratory control (metabolic acidosis, ASA, toxicity)
Psychiatric
Anxiety/psychosomatic
Chronic dyspnea (wks-mos)
Cardiac causes
Valvular heart disease
Decreased CO
Respiratory causes
Parenchymal lung disease (interstitial disease)
Pulmonary vascular disease (pulmonary HTN, vasculitis)
Pleural disease (effusion)
Gas exchange (infection, emphysema, fibrosis, etc.)
Airway disease – asthma, COPD
Hematologic causes
Severe anemia
Neuromuscular and chest wall disorders
Deconditioning, obesity, pregnancy

Table 2. Differential Diagnosis of Chest Pain

Nonpleuritic	Pleuritic
Pulmonary	Pulmonary
Pneumonia	Pneumonia
PE	PE
Neoplastic	Pneumothorax
Cardiac	Hemothorax
MI	Neoplasm
Myocarditis/pericarditis	TB
Esophageal	Empyema
GERD	Cardiac
Spasm	Pericarditis
Esophagitis	Dressler's syndrome
Ulceration	GI
Achalasia	Subphrenic abscess
Neoplasm	Pancreatitis
Esophageal rupture	MSK
Mediastinal	Costochondritis
Lymphoma	Fractured rib
Thymoma	Myositis
Subdiaphragmatic	Herpes zoster
PUD	
Gastritis	
Biliary colic	
Pancreatic	
Vascular	
Dissecting aortic aneurysm	
MSK	
Costochondritis	
Skin	
Breast	
Ribs	

Table 3. Differential Diagnosis of Hemoptysis**Airway Disease**

Acute or chronic bronchitis
Bronchiectasis
Bronchogenic CA
Bronchial carcinoid tumour

Parenchymal Disease

Pneumonia
TB
Lung abscess
Miscellaneous:
Goodpasture's syndrome
Idiopathic pulmonary hemosiderosis

Vascular Disease

PE
Elevated pulmonary venous pressure:
LVF
Mitral stenosis
Vascular malformation

Miscellaneous

Impaired coagulation
Pulmonary endometriosis

Table 4. Differential Diagnosis of Cough**Airway Irritants**

Inhaled smoke, dusts, fumes
Aspiration
Gastric contents (GERD)
Oral secretions
Foreign body
Postnasal drip

Airway Disease

URTI including postnasal drip and sinusitis
Acute or chronic bronchitis
Bronchiectasis
Neoplasm
External compression by node or mass lesion
Asthma
COPD

Parenchymal Disease

Pneumonia
Lung abscess
Interstitial lung disease

CHF

Drug-induced (e.g. ACE inhibitor)

Adapted from *Principles of Pulmonary Medicine*, 5th edition, SE Weinberger, Copyright (2008), with permission from Elsevier.

Table 5. Differential Diagnosis of Clubbing**Pulmonary**

Cystic fibrosis
Pulmonary fibrosis
Chronic pus in the lung
(bronchiectasis, abscess,
infections, etc.)
Lung CA (primary or mets)
A-V fistula
Solitary fibrous tumour of pleura

Gastrointestinal

IBD (UC, CD)
Chronic infections
Laxative abuse
Polyposis
Malignant tumours
Cirrhosis
Hepatocellular carcinoma

Cardiac

Cyanotic congenital heart disease
Infective endocarditis

Mediastinal

Esophageal CA
Thymoma

Other

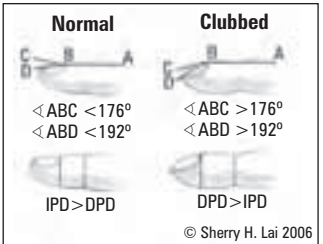
Graves Disease
Thalassemia
Other malignancies
Primary hypertrophic osteoarthropathy

**Most Common Causes of Chronic Cough in Healthy-appearing Patient (cough > 3 months with normal CXR)**

- GERD
- Asthma
- Post-nasal drip
- Post-viral
- ACE inhibitor

**Hemoptysis**

- Most common cause is bronchitis
- 90% of massive hemoptysis is from the bronchial arteries
- Considered "massive" if > 600 cc/24 hours

**Figure 3. Three Signs of Clubbing**

1. Profile Angle (ABC > 176°)
 2. Hyponychial Angle (ABD > 192°)
 3. Phalangeal Depth Ratio (DPD:IPD > 1)
- Adapted from *JAMA* 2001; 286(3):341-7.

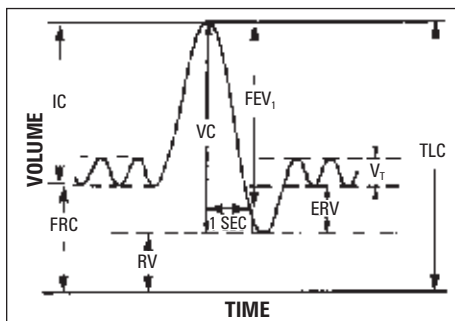


Clubbing is not seen in COPD – if present, think malignancy.

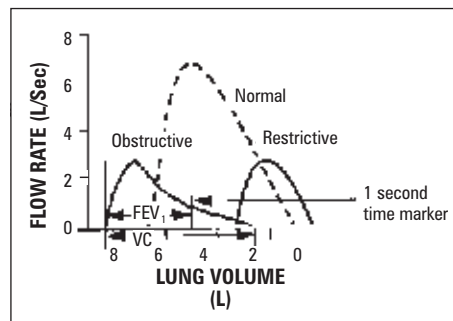
Pulmonary Function Tests (PFTs)



- useful in differentiating the pattern of lung disease (obstructive vs. restrictive) (Table 6)
- assess lung volumes, flow rates, and diffusion capacity (see Figures 4a and 4b below)
- **note:** normal values for FEV₁ are approximately ±20% of the predicted values (for age, sex and height); race may affect predicted values

**Figure 4A. Subcompartments of Lung Volumes**

Adapted from *Principles of Pulmonary Medicine*, 5th edition, SE Weinberger, Copyright (2008), with permission from Elsevier.

**Figure 4B. Expiratory Flow Volume Curves****Obstructive Lung Disease**

- characterized by decreased flow rates (most marked during expiration), air trapping (increased RV/TLC), and hyperinflation (increased FRC, TLC)
- differential diagnosis includes asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), bronchiolitis and bronchiectasis

Restrictive Lung Disease

- characterized by decreased lung compliance and lung volumes
- differential diagnosis includes interstitial lung disease, pleural disease (e.g. pulmonary fibrosis), neuromuscular disease, chest wall disease

**Lung Volumes**

FEV₁ – Forced Expiratory Volume in one second
MMFR – Maximal Mid-Expiratory Flow Rate
FVC – Forced Vital Capacity
FEF – Forced Expiratory Flow Rate
FRC – Functional Residual Capacity
TLC – Total Lung Capacity
VC – Vital Capacity
RV – Residual Volume
Dco – Diffusion Capacity of Carbon Monoxide



Diffusion Capacity of Carbon Monoxide (D_{CO})

D_{CO} decreases with:

1. Decreased surface area (e.g. emphysema)
2. Decreased hemoglobin
3. Interstitial lung disease
4. Pulmonary vascular disease

D_{CO} increases with:

1. Asthma
2. Pulmonary hemorrhage
3. Polycythemia
4. Increased pulmonary blood volume

Table 6. Comparison of Lung Flow and Volume Parameters in Obstructive vs. Restrictive Lung Disease

		Obstructive	Restrictive
Flow Rates	FEV_1/FVC	↓	↑ or N
Lung Volumes	TLC	↑ or N	↓
	RV	↑↑↑↑	↓
	RV/TLC	↑	N
Diffusion Capacity	D_{CO}	↓ or N	↓ or N

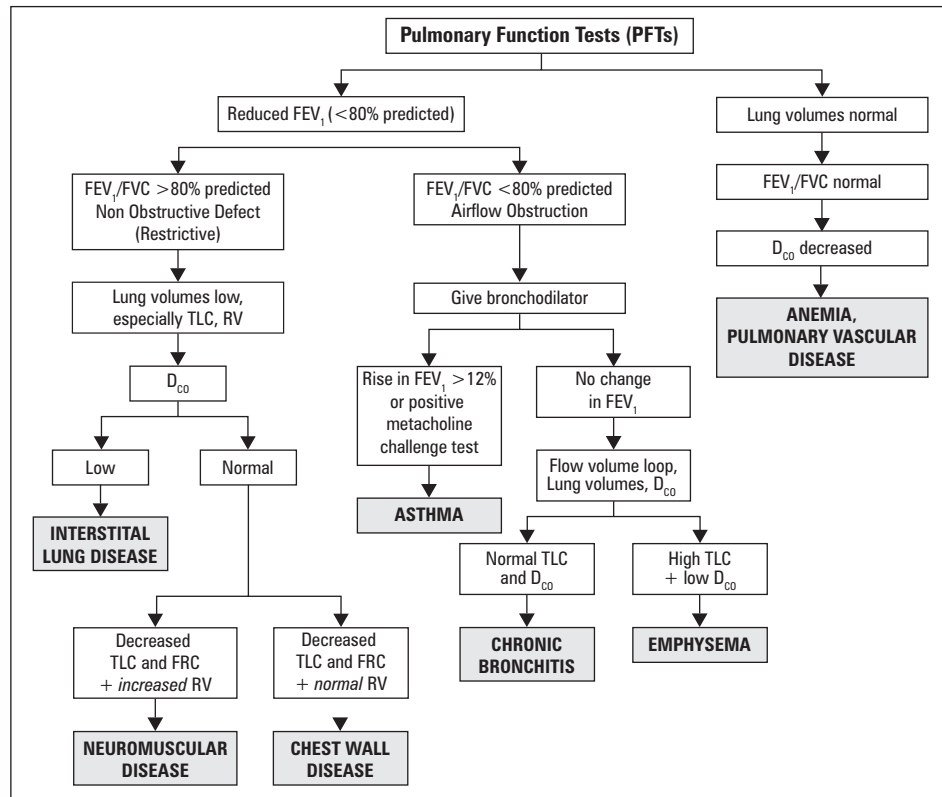


Figure 5. Interpreting PFTs



Chest X-Rays

- see also [Diagnostic Medical Imaging](#), DM4

Table 7. CXR Patterns and Differential Diagnosis

Pattern	Signs	Common DDx
Consolidation ("Airspace disease")	Air bronchogram Silhouette sign Less visible blood vessels	Acute: water (pulmonary edema), pus (pneumonia), blood (hemorrhage) Chronic: neoplasm (lymphoma), inflammatory (eosinophilic pneumonia), granuloma (TB, fungal, sarcoid)
Reticular ("Interstitial disease")	Increased pulmonary markings Honeycombing (IPF)	Interstitial lung disease (IPF, CVD, asbestos, drugs)
Nodular	Cavitary vs. non-cavitary	Cavitary: neoplasm (primary vs. metastatic lung cancer), infectious (TB, fungal), inflammatory (Wegener's, RA) Non-cavitary: above + sarcoid (in HIV), Kaposi's sarcoma

Arterial Blood Gases



- provides information on acid-base and oxygenation status
- see also Nephrology, NP16

Approach to Acid-Base Status

1. Is the pH acidemic (pH <7.35), alkalemic (pH >7.45), or normal (pH 7.35-7.45)?
2. What is the primary disturbance?
 - metabolic: change in HCO_3 and pH in same direction
 - respiratory: change in HCO_3 and pH in opposite direction
3. Has there been appropriate compensation? (Table 8)
 - metabolic compensation occurs over 2-3 days reflecting altered renal HCO_3 production and excretion
 - respiratory compensation through ventilation control of PaCO_2 occurs immediately
 - inadequate compensation may indicate a second acid-base disorder

Table 8. Expected Compensation for Specific Acid-Base Disorders

Disturbance	PaCO_2 (mmHg)	HCO_3 (mmHg)
Respiratory Acidosis		
Acute	↑ 10	↑ 1
Chronic	↑ 10	↑ 3
Respiratory Alkalosis		
Acute	↓ 10	↓ 2
Chronic	↓ 10	↓ 5
Metabolic Acidosis	↓ 1	↓ 1
Metabolic Alkalosis	↑ 5-7	↑ 10

4. If there is metabolic acidosis, what is the anion gap and osmolar gap?
 - anion gap = $[\text{Na}] - ([\text{Cl}] + [\text{HCO}_3])$; normal $\leq 10-15$ mmol/L
 - osmolar gap = measured osmolarity – calculated osmolarity = measured – $(2[\text{Na}] + \text{glucose} + \text{urea})$; normal ≤ 10
5. If anion gap is increased, is the change in bicarbonate the same as the change in anion gap?
 - if not, consider a mixed metabolic picture

DIFFERENTIAL DIAGNOSIS OF RESPIRATORY ACIDOSIS

characterized by increased PaCO_2 secondary to hypoventilation

- respiratory centre depression (decreased RR)
 - drugs (anesthesia, sedatives, narcotics)
 - trauma
 - increased ICP
 - encephalitis
 - stroke
 - central apnea
 - supplemental O_2 in chronic CO_2 retainers (i.e. COPD)
- neuromuscular disorders (decrease TV)
 - myasthenia gravis
 - Guillain-Barré syndrome
 - poliomyelitis
 - muscular dystrophies
 - ALS
 - myopathies
 - chest wall disease (obesity, kyphoscoliosis)
- airway obstruction (asthma, COPD)
- parenchymal disease
 - COPD
 - pulmonary edema
 - pneumothorax
 - pneumonia
 - interstitial lung disease (late stage)
 - acute respiratory distress syndrome (ARDS)
- mechanical hypoventilation (inadequate mechanical ventilation)

DIFFERENTIAL DIAGNOSIS OF RESPIRATORY ALKALOSIS

characterized by decreased PaCO_2 secondary to hyperventilation

- hypoxemia
 - pulmonary disease (pneumonia, edema, PE, interstitial fibrosis)
 - severe anemia
 - heart failure
 - high altitude



Note: Mixed acid-base disturbances can still have a "normal pH"



Ventilation Failure
Think "Can't Breathe" vs. "Won't Breathe" (increased PaCO_2)

Won't Breathe

- Respiratory centre depression
- Hypothyroidism
- Sleep apnea

Can't Breathe

- Neuromuscular disorders
- Airway obstruction
- Parenchymal disease



Anion Gap Metabolic Acidosis

KARMEL
Ketoacidosis
ASA
Renal failure (uremia)
Methanol
Ethylene glycol
Lactic acidosis



Acidosis \leftrightarrow Hyperkalemia
Alkalosis \leftrightarrow Hypokalemia

- respiratory centre stimulation
 - CNS disorders
 - hepatic failure
 - Gram-negative sepsis
 - drugs (ASA, progesterone, theophylline, catecholamines, psychotropics)
 - pregnancy
 - anxiety
 - pain
- mechanical hyperventilation (excessive mechanical ventilation)
- see **Nephrology**, NP16 for differential diagnosis of metabolic acidosis and alkalosis

Calculation of A-aDO₂ Gradient (Approach to Oxygenation Status)

- A-aDO₂: alveolar-arterial oxygen tension difference
 - oxygen gradient between the alveolus and the pulmonary capillaries
- approach includes:
 1. What is the PaO₂? (normal = 95-100 mmHg)
 2. What is the A-aDO₂ gradient? (normal <15 mmHg)
 - A-aDO₂ = PAO₂ (alveolar) – PaO₂ (arterial) = [FiO₂ (Patm – PH₂O) – PaCO₂/RQ] – PaO₂
 - on room air: FiO₂ = 0.21, Patm = 760 mmHg, PH₂O = 47 mmHg, RQ = 0.8
 - ♦ at sea level: A-aDO₂ = [150 – 1.25(PaCO₂)] – PaO₂
 - the normal A-aDO₂ increases with age
 3. What is the cause of the hypoxemia? (see Figure 7)

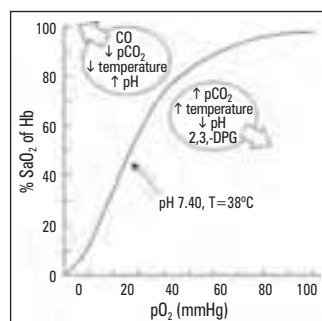
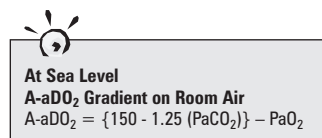


Figure 6. Oxygen-Hb Dissociation Curve

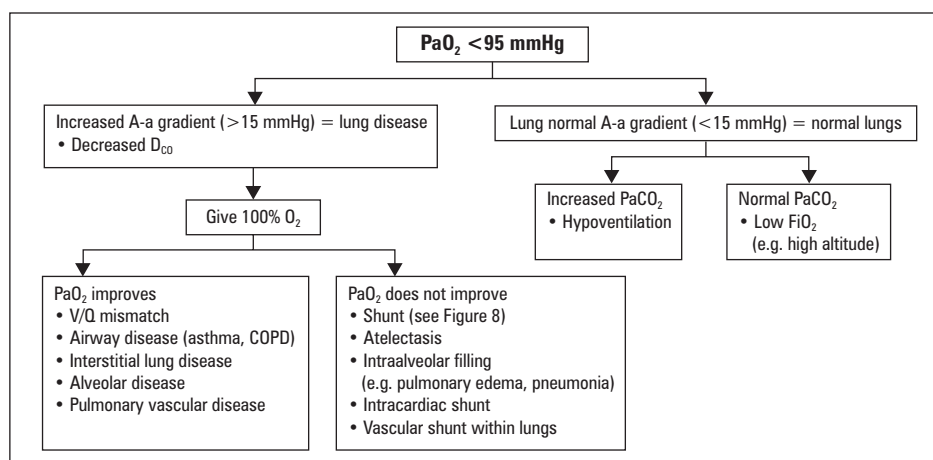


Figure 7. Approach to Hypoxemia

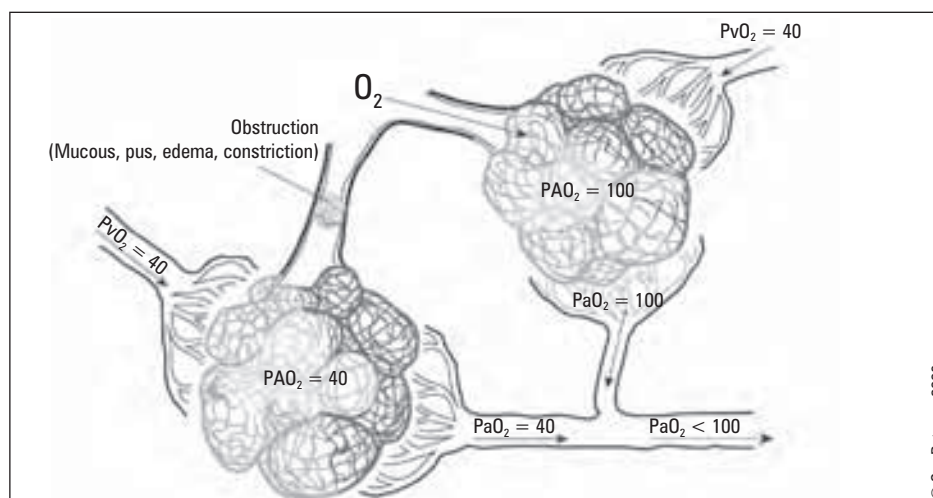


Figure 8. Pathophysiology of Shunt

Diseases of Airway Obstruction



Asthma

Definition

- chronic, inflammatory disorder of the airways resulting in episodes of reversible bronchospasm causing airflow obstruction
- associated with reversible airflow limitation and airway hyper-responsiveness to endogenous or exogenous stimuli

Epidemiology

- common (7-10% of adults), especially in children (10-15%)
- most children with asthma improve significantly in adolescence
- often family history of atopy (asthma, allergic rhinitis, eczema)
- occupational asthma (organic allergies, isocyanates, animals, etc.)

Etiology and Pathophysiology

- acute asthma: airway obstruction → V/Q mismatch → hypoxemia → increased ventilation → decreased PaCO₂ → increased pH and muscle fatigue → decreased ventilation, increased PaCO₂/decreased pH

Triggers

- URTIs, allergens (pet dander, house dusts, moulds), irritants (cigarette smoke, air pollution), drugs (NSAIDs, beta-blockers), preservatives (sulphites, MSG), other (emotion/anxiety, cold air, exercise, GERD)

Signs and Symptoms

- dyspnea, wheezing, chest tightness, cough (especially nocturnal), sputum production
- symptoms can be paroxysmal or persistent

Table 9. Important Signs and Symptoms in Acute Asthma

Red Flags	Respiratory Distress
Fatigue	Nasal flaring, tracheal tug
Diminished expiratory effort	Inability to speak
Cyanosis	Accessory muscle use, intercostal indrawing
Silent chest	Pulsus paradoxus
Decreased LOC	

Adapted from CMAJ 1999; 161(11 Suppl):S1-61

Table 10. Risk Factors Indicating Poor Asthma Control

Previous Non-Fatal Episodes	Ominous Signs and Symptoms
Loss of consciousness during asthma attack	Night time symptoms >1 night/week
Frequent ER visits	Silent chest
Prior intubation	FEV ₁ or PEF (peak expiratory flow) <60%
ICU admission	Limited activities of daily living
	Use of beta ₂ -agonists >3 times/day

Adapted from CMAJ 1999; 161(11 Suppl):S1-61

Table 11. Criteria for Determining whether Asthma is Well Controlled

Daytime symptoms <4 days/wk	No asthma-related absence from work/school
Night-time symptoms <1 night/wk	Beta ₂ -agonist use <4 times/wk
Normal physical activity	FEV ₁ or PEF >90% of personal best
PEF diurnal variation <10-15%	Mild, infrequent exacerbations

Adapted from CMAJ 2005; 173 (11 Suppl): S4

Investigations

- O₂ saturation
- ABGs
 - decreased PaO₂ during attack (V/Q mismatch)
 - decreased PaCO₂ in mild asthma due to hyperventilation
 - normal or increased PaCO₂ is an ominous sign as patient is no longer able to hyperventilate (worsened airway obstruction or respiratory muscle fatigue)
- PFTs (may not be possible during severe attack; do when stable)
 - spirometry: in asthmatics will have increase in FEV₁ >12% with beta₂-agonist, or >20% with 10-14 days of steroids, or >20% spontaneous variability
 - provocation testing: decrease in FEV₁ >20% with methacholine challenge (to confirm diagnosis when bronchodilator response not significant)
 - peak flow



Airway Obstruction (decreased FEV₁)

- Asthma
- COPD (chronic bronchitis, emphysema)
- Bronchiectasis
- Cystic fibrosis



Red Flag
A good predictor of a potential life-threatening attack is excessive consumption of short-acting beta₂-agonists.



Central cyanosis is not detectable until the SaO₂ is <85%.
It is more easily detected in polycythemia and less readily detectable in anemia.



Asthma Triad (Samter's Triad)

- Asthma
- ASA/NSAID sensitivity
- Nasal polyps



Consider LABA for night-time symptoms.

Randomized, Placebo Controlled Trial of Effect of a Leukotriene Receptor Antagonist, Montelukast, on Tapering Inhaled Corticosteroids in Asthmatic Patients
BMJ 1999; 319:87-90

Study: Double blind, randomized, placebo controlled, parallel group, multicentre study with a follow-up of 12 weeks.

Patients: 226 clinically stable patients (mean age 41 yrs, 52% female) with chronic asthma requiring moderate to high doses of corticosteroids for control.

Intervention: Patients were randomized to receive either montelukast 10 mg PO qhs or placebo while undergoing a tapering protocol in which their dose of inhaled corticosteroids was tapered, maintained, or increased (rescue) every 2 weeks based on a standardized clinical score.

Primary Outcomes: Lowest tolerated dose of inhaled corticosteroids.

Results: Patients taking montelukast were able to taper their inhaled corticosteroid dose to a significantly greater degree than those taking placebo (47% vs. 30%, $P=0.046$). In addition, those taking montelukast were significantly less likely to require discontinuation of the tapering protocol due to failure of increased corticosteroid dose/rescue to maintain clinical stability (16% vs. 30%, $P=0.001$, NNT=8).

Conclusion: Montelukast allows significantly greater reduction in the dose of inhaled corticosteroids required to maintain clinical stability in chronic asthmatics formerly requiring moderate to high doses.



Remember to step down therapy to lowest doses which control symptoms and signs of bronchoconstriction.



Natural Progression of COPD

40s Chronic productive cough, wheezing occasionally

50s 1st acute chest illness

60s Dyspnea on exertion, increasing amounts of sputum production, more frequent acute exacerbations

Late Stage Hypoxemia with cyanosis, polycythemia (RBCs), hypercapnia (morning headache), hypoxemia, cor pulmonale



Remember, first line therapy for COPD is smoking cessation



Chronic Treatment for COPD

COPDER

Corticosteroids (inhaled)
 Oxygen

Prevention (vaccines, smoking cessation)

Dilators (AChI's > beta2 agonists)

Experimental (surgery, roflumilast)

Rehabilitation

Treatment

- environmental control: avoid triggers
- patient education: features of the disease, goals of treatment, self-monitoring
- pharmacological therapy
 - symptomatic relief in acute episodes: short-acting beta₂-agonist, anticholinergic bronchodilators, oral steroids, addition of a long acting beta₂-agonist
 - long-term prevention of acute episodes: inhaled/oral corticosteroids, anti-allergic agent, long-acting beta₂-agonist, methylxanthine, leukotriene receptor antagonists (LTRA)

Guidelines for Asthma Management

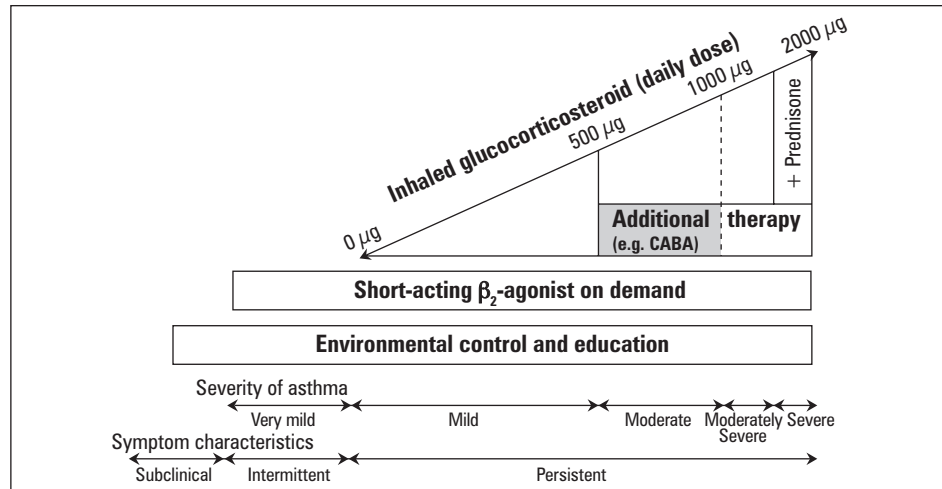


Figure 9. Guidelines for Asthma Management

Adapted from *CMAJ* 1999; 161(11 Suppl):S1-61

Emergency Management of Asthma (see also *Emergency Medicine*, ER31)

1. inhaled beta₂-agonist first line (MDI route and spacer device recommended)
2. add anticholinergic therapy
3. ketamine and succinylcholine for rapid sequence intubation in life-threatening cases
4. SC/IV adrenaline, IV salbutamol if unresponsive
5. all patients admitted to ER for asthma exacerbations should be considered for corticosteroid therapy at discharge

Chronic Obstructive Pulmonary Disease (COPD)

Definition

- characterized by progressive development of irreversible airway obstruction
- 2 subtypes (chronic bronchitis, emphysema): usually coexist to variable degrees in most patients
- course: gradual decrease in FEV₁ over time with episodes of acute exacerbations

Table 12. Clinical and Pathologic features of COPD

Chronic Bronchitis	Emphysema
Defined clinically as: Productive cough on most days for at least 3 consecutive months in 2 successive years Obstruction is due to narrowing of the airway lumen by mucosal thickening and excess mucus	Defined pathologically as: Dilation and destruction of air spaces distal to the terminal bronchiole without obvious fibrosis Decreased elastic recoil of lung parenchyma causes decreased expiratory driving pressure, airway collapse, and air trapping
2 types:	
1) Centriacinar (respiratory bronchioles predominantly affected) <ul style="list-style-type: none"> • Typical form seen in smokers, primarily affects upper lung zones 	
2) Panacinar (respiratory bronchioles, alveolar ducts, and alveolar sacs affected) <ul style="list-style-type: none"> • Responsible for less than 1% of emphysema cases, (alpha-1-antitrypsin deficiency), primarily affects lower lobes 	

Risk Factors

- smoking is the most important risk factor (likelihood ratio of 8.3)
- other risk factors include:
 - environmental factors: air pollution, occupational exposure
 - treatable factors: alpha-1-antitrypsin deficiency, bronchial hyperactivity
 - demographic factors: age, family history, male sex, history of childhood respiratory infections, and low socioeconomic status

Signs and Symptoms**Table 13. Clinical Presentation and Investigations for Chronic Bronchitis and Emphysema**

	Symptoms	Signs	Investigations
Bronchitis (Blue Bloater)	<ul style="list-style-type: none"> • Chronic productive cough • Purulent sputum • Hemoptysis • Mild dyspnea initially 	<ul style="list-style-type: none"> • Cyanotic (2° to hypoxemia and hypercapnia) • Peripheral edema from RVF (cor pulmonale) • Crackles, wheezes • Prolonged expiration if obstructive • Frequently obese 	<p>PFT:</p> <ul style="list-style-type: none"> • ↓ FEV₁, ↓ FEV₁/FVC • N TLC, ↑ or N D_{CO} <p>CXR:</p> <ul style="list-style-type: none"> • AP diameter normal • ↑ bronchovascular markings • Enlarged heart with cor pulmonale
Emphysema (Pink Puffer)	<ul style="list-style-type: none"> • Dyspnea (± exertion) • Minimal cough • Tachypnea • Decreased exercise tolerance 	<ul style="list-style-type: none"> • Pink skin • Pursed-lip breathing • Accessory muscle use • Cachectic appearance due to anorexia and increased work of breathing • Hyperinflation/barrel chest, hyperresonant percussion • Decreased breath sounds • Decreased diaphragmatic excursion 	<p>PFT:</p> <ul style="list-style-type: none"> • ↓ FEV₁, ↓ FEV₁/FVC • ↑ TLC (hyperinflation) • ↑ RV (gas trapping) <p>CXR:</p> <ul style="list-style-type: none"> • ↑ AP diameter • Flat hemidiaphragm (on lateral CXR) • ↓ heart shadow • ↑ retrosternal space • Bullae • ↓ peripheral vascular markings

Treatment of Stable COPD

- prolong survival
 - smoking cessation: nicotine replacement, bupropion (Zyban®), varenicline (Champix®)
 - vaccination: influenza, Pneumovax®
 - home oxygen: to prevent cor pulmonale and decrease mortality if used >15 hrs/day
 - ♦ indications: PaO₂ <55 mmHg; or <60 mmHg with cor pulmonale or polycythemia
- symptomatic relief (no mortality benefit)
 - bronchodilators: mainstay of current drug therapy, used in combination
 - ♦ anticholinergics (e.g. ipratropium bromide, tiotropium bromide)
 - more effective than beta₂-agonists with fewer side effects
 - slower onset of action; take regularly rather than on prn basis
 - ♦ short acting beta₂-agonists (e.g. salbutamol, terbutaline)
 - rapid onset of action
 - significant side effects at high doses (e.g. hypokalemia)
 - ♦ long acting beta₂-agonists (e.g. salmeterol, formoterol)
 - ♦ theophylline – increases collateral ventilation, mucociliary clearance, and may reduce airway inflammation; used as 4th line
 - side effects: nervous tremor, nausea/vomiting/diarrhea, tachycardia, arrhythmias, sleep changes, headache, gastric acid, toxicity
 - corticosteroids
 - ♦ chronic use of systemic glucocorticoids should be avoided
 - ♦ COPD airways are usually inflamed, but not generally responsive to steroids
 - ♦ inhaled steroids shown to improve FEV₁, reduce exacerbations, and possibly improve mortality (TORCH study, NEJM 2007)
 - surgical treatment
 - ♦ lung reduction surgery: resection of emphysematous parts of lung to improve ventilatory function, associated with higher mortality in certain risk groups (FEV₁ <20%)
 - ♦ lung transplant
- others
 - patient education, eliminate respiratory irritants/allergens (occupational/environmental), exercise rehabilitation to improve physical endurance

The Accuracy of Patient History, Wheezing, and Laryngeal Measurements in Diagnosing Obstructive Airway Disease

JAMA 2000; 238(14):1853-57.

Study: Multi-center case-control study.**Population:** 309 patients with known chronic obstructive pulmonary disease (COPD); suspected COPD; and controls.**Intervention:** Various aspects of history and physical exam versus spirometry (FEV₁ and FEV₁/FVC <5th percentile).**Primary Outcome:** Sensitivity, specificity and likelihood ratios (LR) to diagnose COPD.**Results:**

Findings	(+) LR	(-) LR
Smoked >40 pk-years	11.6 (8.3)*	0.9 (0.8)*
Age >45	1.4 (1.3)*	0.5 (0.4)*
Maximum laryngeal height <4 cm	3.6 (2.8)*	0.7 (0.8)*
All combined	58.5 (221)*	0.32 (0.13)*

* Separate LRs for patients self-reporting past history of COPD

† Includes past history of COPD (+LR 7.3, -LR 0.5)

Pulmonary Embolism in Patients with Unexplained Exacerbation of Chronic Obstructive Pulmonary Disease: Prevalence and Risk Factors

Ann Intern Med 2006; 144:390-396

Study: Prospective cohort study of 211 patients with COPD (all current and former smokers) who were admitted to hospital for severe exacerbation of their COPD of unknown origin.**Measurements:** All patients received a spiral CT angiogram (CTA) and venous compression ultrasonography of both legs.**Results:** 25% of patients met diagnostic criteria for PE (+ CTA or + U/S).**Conclusions:** Prevalence of PE in patients hospitalized for COPD exacerbation of unknown origin is 25%.

Therefore, all patients presenting to hospital with COPD exacerbation without an obvious cause require a PE workup (leg dopplers or CTA – decision of which to use depends on pre-test probability of the patient).

Non-invasive Positive Pressure Ventilation for Treatment of Respiratory Failure due to Exacerbations of Chronic Obstructive Pulmonary Disease

Cochrane Database Syst Rev 2004; 3:CD004104.

Study: Cochrane Systematic Review. 14 RCTs.**Population:** 758 adult patients with chronic pulmonary disease (COPD) and acute respiratory failure due to a COPD exacerbation.**Intervention:** Usual medical care (UMC) and Non-invasive positive ventilation (NPPV) versus UMC alone.**Primary Outcome:** Treatment failure, mortality, and tracheal intubation.**Results:** The risks for all primary outcomes were reduced with NPPV use: treatment failure (RR 0.48); mortality (RR 0.52); and intubation use (RR 0.61). Length of hospital stay was a significant mean 3.24 days shorter, but no difference between ICU length of stay. There is a small and significant improvement in pH (weight mean difference (WMD)=0.04), PaCO₂ (WMD=-0.40 kPa), and respiratory rate (WMD=-3.08 bpm) within one hour post-treatment with NPPV. Complications associated with treatment were reduced in the NPPV treatment arm (RR 0.38).**Conclusion:** For patients in respiratory failure due to a COPD exacerbation, NPPV is effective in reducing treatment failure, mortality, and need for intubation when used as a first time treatment adjunct to usual medical care.

Effects of Smoking Intervention and the Use of an Inhaled Anticholinergic Bronchodilator on the Rate of Decline of FEV₁

JAMA 1994; 272:1497-1505

Study: Randomized, double-blind, placebo-controlled, multicentre trial with follow-up of 5 years.

Patients: 73,684 otherwise healthy smokers between the ages of 35 and 60 years were screened with spirometry for evidence of mild to moderate airway obstruction (defined as FEV₁:FVC <70%, and FEV₁ of 55-90% of predicted normal). 12,670 (17%) patients met these criteria and were therefore thought to be at high risk for, or indeed be in the early stages of COPD. Application of exclusion criteria yielded a final study population of 5,887 (8%) smokers with evidence of mild to moderate airway obstruction (mean age 48 yrs, 63% male).

Intervention: Patients were randomized to receive one of usual care (UC), smoking intervention and inhaled Atrovent (SIA), or smoking intervention and inhaled placebo (SIP) for 5 years.

Primary Outcomes: Decline in FEV₁ over a 5 year period.

Results: Patients in the smoking intervention groups had significantly smaller declines in FEV₁ than those receiving usual care. FEV₁ results were most striking at 1 year with a mean decrease of 34.3 mL in the UC group and mean increases of 11.2 and 38.8 mL in the SIP and SIA groups, respectively ($p < 0.005$). Between 1 year and 5 years, FEV₁ declined at similar rates in all three groups (52.3-56.2 mL/yr). However, subgroup analysis revealed that quitters in the SIP group who remained abstinent throughout the study's 5 year follow-up experienced a cumulative decline in FEV₁ of only 72 mL in the same period, compared with a cumulative decline of 301 mL in those who continued to smoke. The small benefit associated with Atrovent was reversible with discontinuation, and therefore did not impact the long-term decline in FEV₁.

Conclusion: Spirometry is an effective screening method for the detection of early COPD. Smoking intervention programs can significantly reduce the decline in FEV₁ in this population. Atrovent did not impact the long-term decline in FEV₁.



Remember to step down therapy to lowest doses which control symptoms/signs of bronchoconstriction.



Complications of COPD

- Chronic hypoxemia
- Pulmonary hypertension from vasoconstriction
- Cor pulmonale

Influenza Vaccination in COPD

Chest 2004; 125(6):2011-20

Study: Single centre, randomized, double-blinded, placebo-controlled trial.

Patients: 125 patients with COPD, stratified by FEV₁ into mild, moderate and severe COPD.

Intervention: Influenza vaccination.

Main Outcomes: Number of episodes and severity of acute respiratory illness, influenza-related and total.

Results: Influenza vaccinated patients experienced 6.8 influenza-related acute respiratory illnesses per 100 patient-years while those in the placebo group experienced 28.1 influenza-related acute respiratory illnesses per 100 patient-years (RR 0.24, $p = 0.005$). This reduction held for all subgroups of FEV₁ level. No effect was seen on the total number of acute respiratory illnesses.

Conclusion: Influenza vaccination is effective in reducing the number of influenza-related illnesses in COPD patients, but not in other acute respiratory illness.

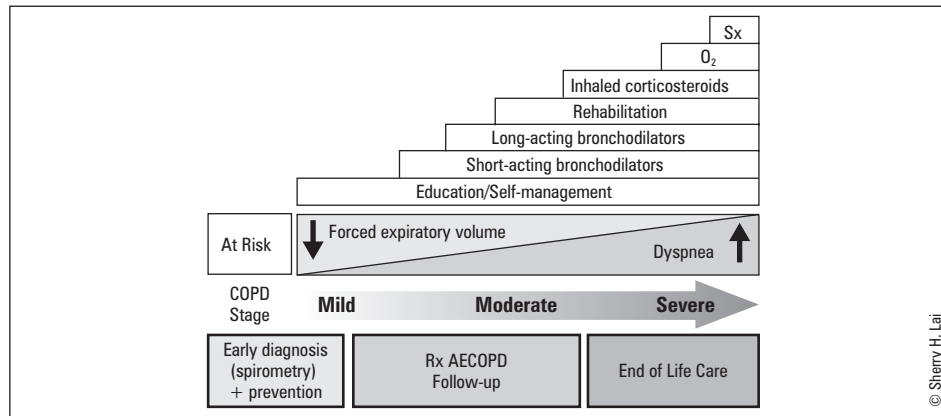


Figure 10. Guidelines for COPD Management

Adapted from Canadian Thoracic Society Recommendations for Management of COPD. (2003). *Can Respir J* 2003; (Suppl A):17A

Acute Exacerbations of COPD

- definition
 - episode of increased dyspnea, coughing, increase in sputum volume or purulence
- etiology: viral URTI, bacteria, air pollution, CHF, PE, MI must be considered
- management
 - assess ABCs, consider assisted ventilation if decreasing LOC or poor ABGs
 - supplemental O₂ (controlled FiO₂): target 88-92% SaO₂ for CO₂ retainers
 - bronchodilators by nebulizer
 - ♦ short acting beta₂-agonists used concurrently with anticholinergics
 - ♦ salbutamol and ipratropium bromide via nebulizers x 3 back-to-back
 - systemic corticosteroids: IV solumedrol or oral prednisone
 - antibiotics: often used to treat precipitating infection
 - ♦ indications (2 out of 3): increased SOB, increased sputum, or increased sputum purulence (change in colour)
 - post exacerbation: rehab with general conditioning to improve exercise tolerance
- ICU admission
 - for life threatening exacerbations
 - ventilatory support
 - ♦ non-invasive: NIPPV, BiPAP
 - ♦ conventional mechanical ventilation

Prognosis in COPD

- complications
 - secondary polycythemia due to hypoxemia
 - pulmonary hypertension due to reactive vasoconstriction 2° to hypoxemia
 - cor pulmonale from chronic pulmonary HTN
 - pneumothorax due to rupture of emphysematous bullae
- prognostic factors
 - severity of airflow limitation (FEV₁) is the single best predictor
 - development of complicating factors such as hypoxemia or cor pulmonale
- 5-year survival
 - FEV₁ <1 L = 50%
 - FEV₁ <0.75 L = 33%
- BODE index for risk of death in COPD
 - greater score indicates higher probability that the patient will die from COPD; score can also be used to predict hospitalization
 - 10 point index consisting of four factors:
 - ♦ body mass index (BMI): <21 (+1 point)
 - ♦ obstruction (FEV₁): 50-64% (+1), 36-49% (+2), <35% (+3)
 - ♦ dyspnea (MMRC scale): walks slower than people of same age on level surface, stops occasionally (+1), stops at 100 yards or a few minutes on the level (+2), too breathless to leave house or breathless when dressing/undressing (+3)
 - ♦ exercise capacity (6 minute walk distance): 250-349 m (+1), 150-249 m (+2), <149 m (+3)

Bronchiectasis

Definition

- an irreversible dilatation of airways due to inflammatory destruction of airway walls resulting from persistently infected mucus
- usually affects medium sized airways
- *P. aeruginosa* is the most common pathogen

Table 14. Etiology and Pathophysiology of Bronchiectasis

Obstruction	Post-infection (results in dilatation of bronchial walls)	Impaired defenses (leads to interference of drainage, chronic infections, and inflammation)
Tumours	Pneumonia	Hypogammaglobulinemia
Foreign bodies	TB	CF
Thick mucus	Measles	Defective leukocyte function
	Pertussis	Ciliary dysfunction (Kartagener's syndrome: bronchiectasis, sinusitis, situs inversus)
	Allergic bronchopulmonary aspergillosis	
	MAC (mycobacteria avium complex)	

Signs and Symptoms

- chronic cough, purulent sputum (but 10-20% have a dry cough), hemoptysis (can be massive), recurrent pneumonia, local crackles (inspiratory and expiratory), wheezes
- clubbing
- often difficult to differentiate from chronic bronchitis

Investigations

- PFTs: often demonstrate obstructive pattern but may be normal
- CXR
 - nonspecific: increased markings, linear atelectasis, loss of volume in affected areas
 - specific: "tram tracking" – parallel narrow lines radiating from hilum, cystic spaces, honeycomb like structures
- high-resolution thoracic CT (diagnostic, gold standard):
 - 87-97% sensitivity, 93-100% specificity
 - "signet ring": dilated bronchi with thickened walls where diameter bronchus > diameter of accompanying artery
- sputum cultures (routine + AFB)
- serum Ig levels
- sweat chloride if cystic fibrosis suspected (upper zone predominant)

Treatment

- vaccination: influenza and Pneumovax®
- antibiotics (oral, IV, inhaled) – routinely used for mild exacerbations, driven by sputum sensitivity; macrolides may be used chronically for an anti-inflammatory effect
- inhaled corticosteroids – decrease inflammation and improve FEV₁
- oral corticosteroids for acute, major exacerbations
- chest physiotherapy, breathing exercises, physical exercise
- pulmonary resection: in severe cases where medical therapy fails

Cystic Fibrosis (CF)

- see also *Pediatrics*, P94

Pathophysiology

- chloride transport dysfunction: thick secretions from exocrine glands (lung, pancreas, skin, reproductive organs) and blockage of secretory ducts

Clinical Features

- results in severe lung disease, pancreatic insufficiency, diabetes and azospermia
- other manifestations include meconium ileus in infancy, distal ileal obstruction in adults, sinusitis, liver disease
- usually presents in childhood with recurrent lung infections that become persistent and chronic
- chronic lung infections
 - S. aureus*: early
 - P. aeruginosa*: most common
 - B. cepacia*: worse prognosis but less common
 - Aspergillus fumigatus*

Investigations

- sweat chloride test
 - increased concentrations of sodium chloride and potassium (chloride >60 mmol/L is diagnostic in children)
 - heterozygotes have normal sweat tests (and no symptoms)
- PFTs
 - characteristic of obstructive airway disease
 - early: only small airways will be affected
 - late: characteristics of obstructive disease with airflow limitation, hyperinflation, gas trapping, decreased DL_{co} (very late)
- ABGs
 - hypoxemia, hypercapnia later in disease with eventual respiratory failure and cor pulmonale
- CXR
 - hyperinflation, increased pulmonary markings (especially involving upper lobes)

Oral Prednisone for COPD Exacerbation

NEJM 2003; 348:2618-25

Study: Randomized, double-blind, placebo-controlled trial with 30 day follow-up

Patients: 147 patients (mean age 69 y, 97% male, 97% white) with COPD, presenting to the ER with at least 2 of the following: recent increase in breathlessness, sputum volume, or sputum purulence. Inclusion criteria also included a smoking history of ≥15 pack-years, and irreversible airflow obstruction in the ER (FEV₁/FVC ≤0.70). Exclusions included patients with asthma or atopy, recent oral or IV steroid use, chest x-ray consistent with pneumonia or CHF, and those requiring admission to hospital.

Intervention: All patients received 10 days of broad-spectrum antibiotics, plus inhaled albuterol and ipratropium bromide for 30 days. Patients were randomized to receive 40 mg prednisone x 10 days, or placebo.

Main Outcomes: Relapse defined as unscheduled visit to a physician or return to ER for worsening SOB within 30 days.

Results: Oral prednisone significantly reduced the rate of relapse at 30 days (27% vs. 43%, p=0.05). Prednisone prolonged the time to relapse (p=0.04). Increased appetite, weight gain, and insomnia were more prevalent in the prednisone group.

Conclusion: In COPD patients discharged from the ER with COPD exacerbation, a 10-day course of oral prednisone offers a small advantage over placebo in preventing relapse.

Treatment

- chest physiotherapy and postural drainage
- bronchodilators (salbutamol ± ipratropium bromide)
- inhaled mucolytic (reduces mucus viscosity)
- inhaled tobramycin
- antibiotics (e.g. ciprofloxacin)
- lung transplant

Prognosis

- depends on: infections, FEV₁, acute pulmonary exacerbations, lung transplant vs. non-lung transplant



Interstitial Lung Disease (ILD)

Pathophysiology

- inflammatory process in the alveolar walls → thickening and possible destruction of pulmonary vessels, and fibrosis of interstitium leading to:
 - decreased lung compliance (increased or normal FEV₁/FVC)
 - decreased lung volumes (decreased TLC, decreased VC, decreased RV)
 - impaired diffusion (decreased D_{co})
 - hypoxemia usually without hypercapnia due to V/Q mismatch
 - pulmonary HTN and cor pulmonale occur with advanced disease secondary to hypoxemia and blood vessel destruction

Table 15. Causes of Interstitial Lung Disease Classified by Distribution

Upper Lung Disease	Lower Lung Disease
Farmer's lung	Bronchiolitis obliterans with organizing pneumonia (BOOP)
Ankylosing spondylitis	Asbestosis
Sarcoidosis	Drugs (nitrofurantoin, hydralazine, INH, amiodarone, many chemo drugs)
Silicosis	Rheumatologic disease
TB	Aspiration
Eosinophilic granuloma (histiocytosis)	Scleroderma
Neurofibromatosis	Hamman Rich (interstitial pulmonary fibrosis)



In Interstitial Lung Disease Think **FASSTEN** and **BAD RASH** (see Table 15)

Etiology

- >100 known disorders can cause interstitial lung disease
- majority due to unknown agents or cause
- divided into 2 major categories: unknown etiology and known etiology

Table 16. Interstitial Lung Diseases

UNKNOWN ETIOLOGY		
Idiopathic pulmonary fibrosis	Other idiopathic interstitial pneumonias including:	
Sarcoidosis	NSIP (nonspecific interstitial pneumonia)	
Langerhans-cell histiocytosis (histiocytosis X)	LIP (lymphocytic interstitial pneumonia)	
Lymphangioleiomyomatosis	COP (cryptogenic organizing pneumonia AKA BOOP)	
Pulmonary infiltrates with eosinophilia (PIE syndromes)		
KNOWN ETIOLOGY		
ILD Associated With	ILD Associated With Drugs or	Inherited Disorders
Systemic Rheumatic Disorders	Treatments	Familial idiopathic pulmonary fibrosis
Scleroderma	Antibiotics (nitrofurantoin)	Neurofibromatosis
Rheumatoid arthritis	Anti-inflammatory agents (methotrexate)	Tuberous sclerosis
SLE	Cardiovascular drugs (amiodarone)	Gaucher's disease
Polymyositis/dermatomyositis	Antineoplastic agents (chemotherapy agents)	
Mixed connective tissue disease	Illicit drugs	Alveolar Filling Disorders
	Radiation	Chronic eosinophilic pneumonia
Environment/Occupation Associated ILD	ILD Associated With Pulmonary	Goodpasture's syndrome
Organic dusts (hypersensitivity pneumonitis)	Vasculitis	Diffuse alveolar hemorrhage
Farmer's lung	Wegener's granulomatosis	Pulmonary alveolar proteinosis
Air conditioner/humidifier lung	Churg-Strauss syndrome	
Bird breeder's lung	Hypersensitivity vasculitis	
Inorganic dusts (pneumoconiosis)	Necrotizing sarcoid granulomatosis	
Silicosis	Idiopathic pulmonary hemosiderosis	
Asbestosis		
Coal workers' pneumoconiosis		
Berylliosis		
Gases/fumes/vapours		

Signs and Symptoms

- SOB, especially on exertion
- dry crackles
- nonproductive cough
- cyanosis
- clubbing (especially in IPF and asbestosis)
- features of cor pulmonale
- note that signs and symptoms vary with underlying disease process
 - e.g. sarcoidosis is seldomly associated with crackles and clubbing

Investigations

- CXR/high resolution CT
 - decreased lung volumes, reticular, nodular, or reticulonodular pattern (nodular <3 mm), Kerley B lines, hilar/mediastinal adenopathy
 - diffuse ground-glass appearance early in disease progresses to honey-combing late in disease
 - DDx: pulmonary fibrosis, interstitial pulmonary edema (CHF), PCP, TB (miliary), sarcoidosis, pneumoconiosis, lymphangitic carcinomatosis
 - DDx of cystic lesions: end-stage emphysema, pulmonary Langerhans-cell histiocytosis, lymphangioleiomyomatosis
- PFTs
 - restrictive pattern: decreased lung volumes (VC and TLC) and compliance
 - normal or increased FEV₁/FVC (>70-80%), i.e. flow rates are often normal or high when corrected for absolute lung volume
 - D_{CO} decreased due to V/Q mismatch less surface area for gas exchange ± pulmonary vascular disease
- ABGs
 - initially may be normal
 - with progression of disease, hypoxemia and decreased PaCO₂ may be present
- Other
 - bronchoscopy, bronchoalveolar lavage, lung biopsy
 - c-ANCA (Wegener's), anti-GBM (Goodpasture's), ESR, ANA (lupus), RF (RA), serum-precipitating antibodies to inhaled organic antigens (hypersensitivity pneumonitis)



The CXR can be normal in up to 15% of patients with interstitial lung disease.



Characteristic CT Findings in ILD
 "ground glass" – early ILD
 "honey combing" – late ILD, especially IPF

Unknown Etiologic Agents

Idiopathic Pulmonary Fibrosis (IPF)

Definition

- a diagnosis of exclusion
- also known as cryptogenic fibrosing alveolitis or usual interstitial pneumonitis (UIP)
- DDx:
 - nonspecific interstitial pneumonitis (NSIP)
 - desquamative interstitial pneumonitis (DIP)
 - lymphocytic interstitial pneumonitis (LIP) – usually 2° to immune conditions such as HIV, Sjögren's, common variable immunodeficiency



IPF Prevalence
 Age 35-44: 2-7 per 100 000
 Age >75: 175 per 100 000

Signs and Symptoms

- commonly presents over age 50, incidence rises with age; males > females
- dyspnea on exertion, nonproductive cough, constitutional symptoms, late inspiratory fine crackles at lung bases, clubbing

Investigations

- labs (nonspecific): ESR, ANA, RF
- CXR: reticular or reticulonodular pattern in lower lung, no hilar adenopathy, cystic or honeycombing (late, poor prognosis)
- high resolution CT: reticular markings, honeycombing (late), ground glass typically not prominent in true IPF
- biopsy: exclude granulomas, helpful if CT not classic

Treatment

- O₂, steroids ± immunosuppressants
- lung transplantation if refractory to medical therapy
- mean survival of 3 to 5 years after diagnosis

Sarcoidosis

Definition

- idiopathic non-infectious granulomatous multi-system disease with lung involvement in 90%
- characterized pathologically by non-caseating granulomas
- proposed triggers include infectious, allergic, and environmental exposures (neither genetic nor specific triggers have been established)

Epidemiology

- typically affects young and middle-aged patients
- higher incidence and more severe disease among black North Americans

Signs and Symptoms

- can be asymptomatic or present with cough, dyspnea, fever, arthralgia, malaise, erythema nodosum, chest pain
- chest exam usually normal
- common extrapulmonary manifestations
 - cardiac (arrhythmias, sudden death)
 - eye involvement (anterior uveitis)
 - skin involvement (skin papules, erythema nodosum, lupus pernio)
 - peripheral lymphadenopathy
 - arthralgia
 - hepatomegaly
- less common extra-pulmonary manifestations involve bone, CNS and kidney
- two acute sarcoid syndromes
 - Lofgren's syndrome: fever, erythema nodosum, bilateral hilar lymphadenopathy, arthralgias
 - Heerfordt-Waldenstrom syndrome: fever, parotid enlargement, anterior uveitis, facial nerve palsy



Sarcoid is usually silent on auscultation.

Investigations

- CBC (cytopenias from marrow involvement)
- serum lytes, creatinine, hypercalcemia, hypercalciuria due to vitamin D retention by granulomas
- hypergammaglobulinemia, RF positive
- elevated serum ACE (non-specific)
- CXR: predominantly nodular opacities especially in upper lung zones ± hilar adenopathy
- ABG: normal, or hypoxemia and hypocapnia
- PFTs: normal, obstructive pattern, restrictive pattern with normal flow rates and decreased D_{co}
- ECG: to rule out arrhythmias
- slit-lamp eye exam: to rule out uveitis



Most common presentation: asymptomatic CXR finding

Diagnosis

- biopsy
 - transbronchial lung biopsy or mediastinoscopic lymph node biopsy for granulomas
 - in ~75% of cases, transbronchial biopsy shows granulomas in the parenchyma even if the CXR is normal

Staging

- radiographic, based on CXR
 - Stage 0: normal radiograph
 - Stage I: bilateral hilar lymphadenopathy ± right paratracheal lymphadenopathy
 - Stage II: bilateral hilar lymphadenopathy and diffuse interstitial disease
 - Stage III: interstitial disease only (reticulonodular pattern or nodular pattern)
 - Stage IV: pulmonary fibrosis (honeycombing)

Treatment

- 85% of stage I resolve spontaneously
- 50% of stage II resolve spontaneously
- steroids for symptoms, declining lung function, hypercalcemia, or involvement of eye, CNS, kidney, or heart (not for abnormal CXR alone)
- methotrexate or other immunosuppressives occasionally used

Prognosis

- approximately 10% mortality secondary to progressive fibrosis of lung parenchyma

Known Etiologic Agents

Hypersensitivity Pneumonitis

- also known as extrinsic allergic alveolitis
- caused by intense/repeated inhalation and sensitization to certain organic agents
- non-IgE mediated inflammation of lung parenchyma (acute, subacute, and chronic forms)
- lymphocytic inflammation and granulomas present, airway centred
- exposure usually related to occupation or hobby
 - Farmer's Lung (*Thermophilic actinomycetes*)
 - Bird Breeder's/Bird Fancier's Lung (*Chlamydia psittaci* in bird droppings)
 - Humidifier Lung (*Aureobasidium pullulans*)
 - Sauna Taker's Lung (*Aureobasidium spp.*)

Signs and Symptoms

- acute presentation: (4-6 hours after exposure)
 - dyspnea, cough, fever, chills, malaise (lasting 18-24 hrs)
 - PFTs: modestly and transiently restrictive
 - CXR: diffuse infiltrates
 - type III (immune complex) reaction
- subacute presentation: more insidious onset than acute presentation
- chronic presentation
 - insidious onset
 - dyspnea, cough, malaise, anorexia, weight loss
 - PFTs: progressively restrictive
 - CXR: predominantly upper lobe, nodular/reticulonodular pattern
 - type IV (cell mediated, delayed hypersensitivity) reaction (see [Rheumatology](#), R16)
- in both acute and chronic reactions, serum precipitins may be detectable (neither sensitive nor specific)

Treatment

- goal is to prevent chronic fibrotic changes
- early diagnosis: avoidance of further exposure is critical as chronic changes are irreversible
- systemic corticosteroids can relieve symptoms in acute phase
- steroids for persistent disease

Pneumoconioses

- reaction to inhaled inorganic dusts 0.5-5 μM in size
- no effective treatment, therefore key is exposure prevention through the use of protective equipment

Asbestosis

- population at risk: insulation, shipyard, construction, brake linings, pipe fitters, plumbers
- slowly progressive diffuse interstitial fibrosis from dose-related inhalation of asbestos
- etiology: usually >10-20 yrs of exposure; may develop with shorter but heavier exposure; typically prolonged interval (20-30 yrs) between exposure and clinical manifestations of disease
- signs and symptoms
 - insidious onset
 - SOB on exertion usually first symptom with increased dyspnea as disease progresses
 - cough: paroxysmal, non-productive
 - fine end-respiratory crackles (increased at bases)
 - clubbing (much more likely in asbestosis than silicosis or coal workers' pneumoconioses), edema, jugular venous distention
- investigations: CXR
 - lower > upper lobe
 - early: fibrosis with linear streaking
 - later: cysts and honeycombing
 - asbestos exposure can also cause pleural and diaphragmatic plaques (\pm calcification), pleural effusion, round atelectasis
- microscopic examination reveals ferruginous bodies: yellow-brown rod-shaped structures which represent asbestos fibres coated in macrophages
- complications: asbestos exposure increases risk of bronchogenic CA and malignant mesothelioma
 - risk of lung cancer dramatically increased for smokers
- treatment:
 - removal from exposure
 - smoking cessation, proper nutrition, exercise
 - home oxygen PRN
 - treatment of respiratory infections, annual influenza and pneumococcal vaccinations



Diaphragmatic plaques are highly suggestive of asbestosis.



CXR Fibrotic Patterns

Asbestosis: lower > upper lobes
Silicosis: upper > lower lobes
Coal: upper > lower lobes



Remember to involve occupational health at place of work for data collection and treatment plan.
Also counsel re: worker's insurance as per jurisdiction (e.g. WSIB in Ontario).

Silicosis

- at risk population: sandblasters, rock miners, stone cutters, quarry and highway workers
- etiology: generally requires >20 years exposure; may develop with much shorter but heavier exposure
- signs and symptoms: dyspnea, cough and wheezing
- investigations: CXR
 - upper > lower lobe
 - early: nodular disease (simple pneumoconiosis), lung function usually normal
 - late: nodules coalesce into masses (progressive massive fibrosis)
- when nodules become larger and coalesce into masses, disease has changed from simple silicosis to complicated silicosis (progressive massive fibrosis)
- possible hilar lymph node enlargement (frequently calcified), especially “egg shell” calcification
- complications: mycobacterial infection (e.g. TB)
- treatment: prevention, removal from exposure, treat associated TB if present, supportive measures (oxygen, bronchodilators), lung transplant

Coal Worker’s Pneumoconiosis (CWP)

- at risk population: coal workers, graphite workers
- etiology: coal and silica, coal is less fibrogenic than silica
- pathologic hallmark is coal macule:
 - coal dust surrounded by minimal tissue reaction and focal emphysema
 - found around respiratory bronchioles
- simple CWP
 - no signs or symptoms
 - CXR: multiple nodular opacities, mostly upper lobe
 - respiratory function well preserved
- complicated CWP (also known as progressive massive fibrosis)
 - dyspnea
 - CXR: opacities larger and coalesce
- course: few patients progress to complicated CWP
- Caplan’s syndrome: rheumatoid arthritis and CWP present as larger nodules
- treatment: minimize future exposure, cardiopulmonary rehabilitation, follow periodically

ILD Associated with Drugs or Treatments

Drug-Induced

- antineoplastic agents: bleomycin, mitomycin, busulfan, cyclophosphamide, methotrexate, chlorambucil, BCNU (carmustine)
- antibiotics: nitrofurantoin, penicillin, sulfonamide
- cardiovascular drugs: amiodarone, tocainide
- anti-inflammatory agents
- gold salts
- illicit drugs (heroin, methadone)

Radiation-Induced

- early pneumonitis: approximately 6 weeks post-exposure
- late fibrosis: 6-12 months post-exposure
- infiltration conforms to the shape and field of the irradiation



Pulmonary Vascular Disease

Pulmonary Hypertension

Definition

- mean pulmonary arterial pressure >25 mmHg at rest and >30 mmHg with exercise, or a systolic pulmonary artery pressure of >40 mmHg at rest
- in the past, pulmonary hypertension was classified as primary or secondary pulmonary hypertension, but this classification was modified to a more clinically useful, treatment based classification (Table 17)

Table 17. Diagnostic Classification of Pulmonary Hypertension (WHO 1998)

Classification	Causes
Pulmonary arterial hypertension	Primary pulmonary hypertension – sporadic vs. familial related to: Collagen vascular disease (scleroderma, SLE, RA) Congenital systemic-to-pulmonary shunts (Eisenmenger syndrome) Portopulmonary hypertension HIV infection Drugs and toxins (e.g. anorexigens)
Pulmonary venous hypertension	Left-sided atrial or ventricular heart disease (e.g. LV dysfunction) Left-sided valvular heart disease (e.g. aortic stenosis, mitral stenosis) Pulmonary veno-occlusive disease Extrinsic compression of central pulmonary veins (tumour, adenopathy, fibrosing mediastinitis)
Associated with disorders of the respiratory system and/or hypoxemia	Parenchymal lung disease (COPD, interstitial fibrosis, cystic fibrosis) Chronic alveolar hypoxia (chronic high altitude, alveolar hypoventilation disorders, sleep disordered breathing)
Due to chronic thrombotic and/or embolic disease	Thromboembolic obstruction of proximal pulmonary arteries Obstruction of distal pulmonary arteries – PE (thrombus, foreign material, tumour, schistosomiasis, in situ thrombosis, sickle cell disease)
Due to disorders directly affecting the pulmonary vasculature	Inflammatory (sarcoidosis, schistosomiasis) Pulmonary capillary hemangiomatosis

Mechanisms of Pulmonary Hypertension

- the approach is simplified as some causes could fall under more than one mechanism
- hypoxic vasoconstriction
 - chronic hypoxia causes pulmonary vasoconstriction by a variety of actions on the pulmonary artery endothelium and smooth muscle cells, such as: down regulation of endothelial nitric oxide synthase and alteration of voltage gated potassium channels leading to vasoconstriction
 - causes: COPD, chronic alveolar hypoxia
- decreased area of pulmonary vascular bed
 - leads to a rise in resting pulmonary arterial pressure
 - causes: collagen vascular disease, HIV infection, drugs and toxins, thrombotic or embolic disease, inflammatory, pulmonary capillary hemangiomatosis, interstitial fibrosis, cystic fibrosis
- volume and pressure overload
 - significant hypertension only occurs with excessive volume overload, since pulmonary artery pressure will not rise in otherwise normal lung until pulmonary blood flow exceeds 2.5 times the basal rate
 - causes: congenital systemic to pulmonary shunts (e.g. VSD, ASD, PDA), portopulmonary hypertension, left-sided heart conditions, pulmonary veno-occlusive disease, extrinsic compression of central pulmonary veins

IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION [AKA PRIMARY PULMONARY HYPERTENSION (PPH)]**Definition**

- pulmonary hypertension in the absence of a demonstrable cause (exclude left-sided cardiac valvular disease, myocardial disease, congenital heart disease, and any clinically significant parenchymal lung disease, systemic connective-tissue, or chronic thromboembolic disease)

Epidemiology

- disease of young women (20-40 years); mean age of diagnosis is 36 years
- most cases are sporadic; familial predisposition in 10% of cases, linked to mutations in BMPR2
- may be associated with the use of anorexic drugs (e.g. Aminorex®, Fenfluramine®), also amphetamines and cocaine

Signs and Symptoms

- exertional dyspnea, fatigue, syncope, exertional chest pain, Raynaud's phenomenon
- see Table 18

Prognosis

- 2-3 year mean survival from time of diagnosis
- survival decreases to approximately 1 year if severe pulmonary HTN or right-heart failure

Guidelines for Vasodilator Response in Pulmonary Arterial HTN

- Evidence for the use of CCBs after a positive vasodilator challenge is limited to patients with IPAH.
- The precise definition about what constitutes a "positive" result is controversial. The latest consensus according to the European Society of Cardiology was that a positive result constitutes a fall of mean PAP pressure of 10 mmHg to less than or equal to 40 WITHOUT a change in cardiac output.
- Best agents to use: NO or epoprostenol (prostacyclin) analogue (best safety profile).
- Those who have a "significant" response (as determined by the criteria in #2) should be treated cautiously with a CCB (nifedipine, diltiazem, amlodipine are good choices, NOT verapamil). Evidence suggests these patients will have improved survivals.

Reference: Badesch et al. Medical Therapy For Pulmonary Arterial Hypertension. ACCP Evidence-Based Clinical Practice Guidelines. Chest 126, Supplement, July, 2004.

Table 18. Signs and Symptoms of Pulmonary Hypertension

Symptoms	Signs
Dyspnea	Loud, palpable P2
Fatigue	RV heave
Substernal chest pain	Right-sided S4 (due to RVH)
Syncope	Systolic murmur (TR)
Symptoms of underlying disease	If RV failure: right sided S3, increased JVP, positive HJR, peripheral edema, TR

Investigations

- CXR: enlarged central pulmonary arteries, cardiac changes due to RV enlargement (filling of retrosternal air space)
- ECG
 - RVH/right-sided strain and RA enlargement, rightward axis deviation
 - R/S ratio >1 in V₁
 - increased P wave amplitude in lead II
 - incomplete or complete R bundle branch block (RVSP)
- 2-D echo doppler assessment of right ventricular systolic pressure
- cardiac catheterization: direct measurement of pulmonary artery pressures
- PFTs to rule out lung disease – DL_{co} usually reduced
- spiral CT to assess lung parenchyma and possible PE
- V/Q scan ± pulmonary angiogram to rule out thromboembolic disease
- serology: ANA positive in 30% of patients with primary pulmonary hypertension

Treatment

- for primary pulmonary hypertension
 - anticoagulation in patients at increased risk for intrapulmonary thrombosis and thromboembolism (anticoagulation of choice is warfarin, target INR approximately 2.0)
 - calcium channel blockers: nifedipine, diltiazem, NOT verapamil
 - vasodilators: oral (sildenafil, bosentan), parenteral (epoprostenol, treprostanil)
 - lung transplantation
- for other forms of pulmonary hypertension
 - continuous oxygen therapy for patients who are hypoxic
 - treat underlying condition before irreversible damage occurs
 - phlebotomy for polycythemia (rarely required)
 - treatment of exacerbating factors: smoking, infection, sleep apnea
 - epoprostenol – beneficial in cardiomyopathy, and NYHA class III-IV symptoms
 - endothelin receptor antagonists (bosentan, sitaxentan)
 - phosphodiesterase inhibitors (sildenafil)



Pulmonary Embolism (PE)

**Virchow's Triad**

- Venous stasis
- Endothelial cell damage
- Hypercoagulable states

Clinical Prediction Rule for Pulmonary Embolism
Thrombosis and Hemostasis 2000; 83(3):416-20
Wells Criteria

Risk Factors	Points
Clinical signs of DVT	3.0
No more likely alternative diagnosis (using H&P, CXR, ECG)	3.0
Immobilization or surgery in the previous 4 weeks	1.5
Previous PE/DVT	1.5
Heart rate >100 beats/min	1.5
Hemoptysis	1.0
Malignancy	1.0

Clinical probability

Low	3%
Intermediate	28%
High	78%
Simplified Wells: >4 likely; ≤4 unlikely for PE	

JAMA 2006

Definition

- lodging of a blood clot in the pulmonary arterial tree with subsequent increase in pulmonary vascular resistance and possible obstruction of blood supply to the lung parenchyma

Etiology and Pathophysiology

- one of the most common causes of preventable death in the hospital
- proximal leg thrombi (popliteal, femoral or iliac veins) are the source of most clinically recognized pulmonary emboli
- thrombi often start in calf, but must propagate into proximal veins to create a sufficiently large thrombus for a clinically significant PE
- fewer than 30% of patients have clinical evidence of DVT (e.g. leg swelling, pain or tenderness)
- always suspect PE if patient suddenly collapses 1-2 weeks after surgery

Risk Factors (Virchow's Triad)

- stasis
 - immobilization: paralysis, stroke, bed rest, prolonged sitting during travel, immobilization of an extremity after fracture
 - obesity, CHF
 - chronic venous insufficiency
- endothelial cell damage
 - post-operative injury, trauma
- hypercoagulable states
 - underlying CA (particularly adenocarcinoma)
 - cancer treatment (chemotherapy, hormonal)
 - exogenous estrogen administration (OCP, HRT)
 - pregnancy, post-partum
 - prior history of DVT/PE, family history
 - nephrotic syndrome

- coagulopathies: Factor V Leiden, Prothrombin 20210A variant, inherited deficiencies of antithrombin/protein C/protein S, antiphospholipid antibody, hyperhomocysteinemia, increased Factor VIII levels, and myeloproliferative disease
- increasing age

Investigations (if highly suspicious, go straight to spiral CT)

- see Emergency Medicine, Figure 13, ER35
- D-dimer (products of thrombotic/fibrinolytic process)
 - ELISA better than latex agglutination
 - D-dimer results alone do not rule in or out DVT/PE
 - consider only in out-patients with low pretest probability
 - need to use in conjunction with leg Dopplers
- spiral CT scan with contrast is both sensitive and specific for PE
 - diagnosis and management uncertain for small filling defects
 - spiral CT may identify an alternative diagnosis if PE is not present
 - CT scanning of the proximal leg and pelvic veins can be done at the same time and may be helpful
- venous duplex ultrasound or doppler
 - with leg symptoms
 - positive test rules in proximal DVT
 - negative test rules out proximal DVT
 - without leg symptoms
 - positive test rules in proximal DVT
 - negative test does not rule out a DVT – patient may have non-occlusive or calf DVT
- ECG
 - findings not sensitive or specific
 - sinus tachycardia most common; may see non-specific ST segment and T wave changes
 - RV strain, RAD, RBBB, S1-Q3-T3 with massive embolization
- CXR
 - frequently normal; no specific features
 - atelectasis (subsegmental), elevation of a hemidiaphragm
 - pleural effusion – usually small
 - Hampton's hump – cone-shaped area of peripheral opacification representing infarction
 - Westermark's sign – dilated proximal pulmonary artery with distal oligemia/decreased vascular markings (difficult to assess without prior films)
 - dilatation of proximal PA – rare
- V/Q scan (very sensitive but low specificity)
 - order scan if
 - CXR normal, no COPD
 - contraindication to CT (contrast allergy, renal dysfunction)
 - avoid V/Q scan if
 - CXR abnormal or COPD
 - inpatient
 - suspect massive PE
 - results
 - normal – excludes the diagnosis of PE
 - high probability – most likely means PE present, unless pre-test probability is low
 - 60% of V/Q scans are nondiagnostic
- echocardiogram
 - little diagnostic value
 - increased RVSP, RV hypokinesis, seen in massive PE
- ABG
 - of NO diagnostic use in PE (insensitive and nonspecific)
 - respiratory alkalosis (due to hyperventilation)

Treatment

- admit for observation (patients with DVT only are often sent home on LMWH)
- oxygen: provide supplemental O₂ if hypoxemic or short of breath
- pain relief: analgesics if chest pain – narcotics or NSAIDs
- acute anticoagulation: therapeutic-dose SC LMWH or IV heparin – start ASAP
 - anticoagulation stops clot propagation, prevents new clots and allows endogenous fibrinolytic system to dissolve existing thromboemboli over months
 - get baseline CBC, INR, aPTT ± renal function ± liver function
 - for SC LMWH: dalteparin 200 U/kg once daily or enoxaparin 1 mg/kg bid – no lab monitoring – avoid or reduce dose in renal dysfunction
 - for IV heparin: bolus of 75 U/kg (usually 5,000 U) followed by infusion starting at 20 U/kg/hr – aim for aPTT 2-3 times control



Evaluation of a Suspected Pulmonary Embolism

Low clinical probability of embolism:

D-dimer (+ve) → CT scan (+ve) → ruled in
 (–ve) decreased (–ve) decreased
 ruled out ruled out

Intermediate or high probability:

CT scan (–ve) → ruled out
 (+ve) decreased
 ruled in

Notes:

- Use D-dimers only if low clinical probability, otherwise, go straight to spiral CT
- If using V/Q scans (CT contrast allergy or renal failure):
 - Negative V/Q scan rules out the diagnosis
 - High probability V/Q scan only rules in the diagnosis if have high clinical suspicion
 - Inconclusive V/Q scan requires leg ultrasound to look for DVT or spiral CT



Classic ECG finding of PE is S1-Q3-T3 (inverted T3), but most commonly see only sinus tachycardia.



Workup for Idiopathic VTE

Thrombophilia Workup: recurrent or idiopathic DVT/PE; age <50, +FHx, unusual location, massive.

Malignancy Workup: 12% of patients with idiopathic VTE will have a malignancy.

Excluding Pulmonary Embolism at Bedside

Ann Intern Med 2001; 135:98-107

Study: Multicentre, prospective cohort study.

Patients: 930 patients with suspected PE at emergency departments at 4 tertiary care hospitals in Canada.

Intervention: A Wells score was used to determine patient's pretest probability (PTP) of pulmonary embolism and then a D-dimer test was performed. Patients with low PTP and a negative D-dimer test had no further testing and the diagnosis of pulmonary embolism was excluded. All other patients had V/Q scanning, and if non-diagnostic, had bilateral deep venous ultrasonography. Further serial ultrasonography and angiography were done depending on the patients PTP and lung-scanning results.

Main outcomes: Diagnosis of pulmonary embolism and the development of thromboembolic events at 3 months follow-up.

Results: One of 759 patients in whom PE was initially ruled out developed a thromboembolic event during follow-up (0.1% [CI 0.0%-0.7%]). One of the 437 patients with negative D-dimers and low clinical PTP developed PE during follow up (NPV 99.5%, CI 99.1-100%).

Conclusion: Managing patients with suspected pulmonary embolism on the basis of PTP and D-dimer results is safe and decreases the need for diagnostic imaging.

Multidetector Computed Tomography for Acute Pulmonary Embolism (PIOPED II Trial)

NEJM 2006; 354(22):2317-27

Study: Multicentre, prospective study investigating accuracy of computed tomography angiography (CTA) alone and combined with venous phase imaging (CTA-CTV).

Patients: 824 patients of several thousand eligible for study received reference diagnosis to confirm absence or presence of PE (V/Q scan, venous compression U/S of lower extremities, and pulmonary digital-subtraction angiography (DSA) if necessary). To confirm absence, patients in whom PE was excluded were telephoned 3-6 months after enrollment. Any deaths were reviewed by an outcome committee. All patients enrolled also underwent clinical assessment of PE (including a Wells score) prior to imaging.

Outcomes: Diagnosis of pulmonary embolism.

Results: 773 of 824 patients had adequate CTAs for interpretation. PE was diagnosed in 192 of the 824 patients. Sensitivity was 83% (150 of 181 patients, 95% CI, 0.76-0.92) and specificity was 96% (567 of 592 patients, 95% CI, 0.93-0.97). However, the predictive value of CTA-CTV varied when clinical pre-test probability was taken into account. PPV of CTA for high, intermediate and low clinical probability were 96% (95% CI, 0.78-0.99), 92% (95% CI, 0.84-0.96), and 58% (95% CI, 0.40-0.73) respectively. NPV of CTA for high, intermediate and low clinical probability were 60% (95% CI, 0.32-0.83), 89% (95% CI, 0.82-0.93), and 96% (95% CI, 0.92-0.98) respectively.

Conclusion: CTA is effective for diagnosing or excluding PE in accordance with assessment of clinical pretest probability. When clinical probability is inconsistent with imaging results, further investigations are required to rule out PE.

- long term anticoagulation
 - warfarin – start the same day as LMWH/heparin – overlap warfarin with LMWH/heparin for at least 5 days and until INR in target range of 2-3 for at least 2 days
 - LMWH instead of warfarin for pregnancy, active cancer, high bleeding risk
- IV thrombolytic therapy
 - if patient has massive PE (hypotension or clinical right heart failure) and no contraindications
 - hastens resolution of PE but may not improve survival or long-term outcome and doubles risk of major bleeding
- interventional thrombolytic therapy
 - massive PE is preferentially treated with catheter directed thrombolysis by an interventional radiologist
 - works better than IV thrombolytic therapy and fewer contraindications
- IVC filter: only if recent proximal DVT + absolute contraindication to anticoagulation
- duration of long-term anticoagulation: individualized, however generally:
 - if reversible cause for PE (surgery, injury, pregnancy, etc.): 3-6 months
 - if PE unprovoked: 6 months to indefinite
 - if ongoing major risk factor (active cancer, antiphospholipid antibody, etc.): indefinite

Thromboprophylaxis

- mandatory for most hospital patients: reduces DVT, PE, all-cause mortality, cost-effective
- start ASAP
- continue at least until discharge or at least 10 days if major orthopaedic surgery

Table 19. VTE Risk Categories and Prophylaxis

Risk Group	Prophylaxis Options
Low thrombosis risk:	
• Medical patients – fully mobile	• No specific prophylaxis
• Surgery – <30 minutes, fully mobile	• Frequent ambulation
Moderate thrombosis risk:	
• Most general, gynecologic, urologic surgery	• LMWH
• Sick medical patients	• Low dose heparin
High thrombosis risk:	
• Arthroplasty, hip fracture surgery	• LMWH
• Major trauma, spinal cord injury	• Fondaparinux
	• Warfarin (INR 2-3)
High bleeding risk:	
• Neurosurgery, intracranial bleed	• TED stockings, pneumatic compression devices
• Active bleeding	• LMWH or low dose heparin when bleeding risk decreases

Pulmonary Vasculitis

Table 20. Pulmonary Vasculitis

Disease	Definition	Pulmonary Features	Extra-pulmonary Features	Investigations	Treatment
Wegener's Granulomatosis	Systemic vasculitis of medium and small arteries	Necrotizing granulomatous lesions of the upper and lower respiratory tract	Focal necrotizing lesions of arteries and veins; Focal glomerulonephritis	CXR: nodules and alveolar opacities c-ANCA Tissue confirmation	Corticosteroids and cyclophosphamide
Churg-Strauss Syndrome (Allergic Granulomatosis and Angiitis)	Multisystem disorder characterized by allergic rhinitis, asthma, and prominent peripheral eosinophilia	Asthma Infiltrates	Life-threatening systemic vasculitis involving the lungs, pericardium and heart, kidneys, skin, and PNS (mononeuritis multiplex)	No specific investigation, peripheral eosinophilia is the most common finding pANCA may be positive	Corticosteroids
Goodpasture's Syndrome	A disorder characterized by diffuse alveolar hemorrhage and glomerulonephritis caused by anti-GBM antibodies, which cross-react with basement membranes of the kidney and lung	Hemoptysis May follow an influenza infection	Anemia	CXR: may see alveolar infiltrates if hemorrhage is profuse ELISA test with anti-GBM antibodies Renal biopsy/indirect immunofluorescence	Acutely: corticosteroids, plasmapheresis Immunosuppressive therapy Severe cases: bilateral nephrectomy

Systemic Lupus Erythematosus, Rheumatoid Arthritis, Scleroderma

See [Rheumatology](#)



Scleroderma is the most common collagen vascular disease to affect the lung.

Diseases of the Mediastinum and Pleura

Mediastinal Masses



Definition

- mediastinum structures that are bound by the thoracic inlet, diaphragm, sternum, vertebral bodies and the pleura
- can be broken down into 3 compartments: anterior, middle and posterior

Etiology and Pathophysiology

- diagnosis is made by location and patient's age
- anterior compartment (sternum to anterior border of pericardium) – more likely to be malignant
 - “Five Ts” (see sidebar), lymphoma, lipoma, pericardial cyst
- middle compartment (anterior to posterior pericardium)
 - pericardial cyst, bronchogenic cyst/tumour, lymphoma, lymph node enlargement, aortic aneurysm
- posterior compartment (posterior pericardium to vertebral column)
 - neurogenic tumours, meningocele, enteric cysts, lymphoma, diaphragmatic hernias, esophageal tumour, aortic aneurysm



Anterior Compartment

5T's

Thymoma

Thyroid enlargement (goiter)

Teratoma

Thoracic aortic aneurysm

Tumours

(lymphoma, parathyroid, esophageal, angiomatous)

Signs and Symptoms

- 50% asymptomatic (mainly benign); when symptomatic, 50% are malignant
- chest pain, cough, dyspnea, recurrent respiratory infections
- hoarseness, dysphagia, Horner's syndrome, facial/upper extremity edema (SVC compression)
- paraneoplastic syndromes (e.g. myasthenia gravis (thymomas))

Investigations

- CXR (compare to previous)
- CT with contrast (anatomic location, density, relation to mediastinal vascular structures)
- MRI – specifically indicated in the evaluation of neurogenic tumours
- ultrasound (best for assessment of structures in close proximity to the heart and pericardium)
- radionuclide scanning – ^{131}I (for thyroid), gallium (for lymphoma)
- biochemical studies – thyroid function, serum calcium, phosphate, PTH, AFP, beta-hCG
- biopsy (mediastinoscopy, percutaneous needle aspiration)

Management

- depends on the diagnosis
- decide if the lesion should be excised (e.g. symptomatic growing benign masses or concerns of malignancy)
- resection via minimally invasive video assisted procedures (bronchogenic cysts, localized neurogenic tumours)
- exploration via sternotomy or thoracotomy
- diagnostic biopsy rather than major operation if mass is likely to be a lymphoma, germ cell tumour, or unresectable invasive malignancy
- \pm post-op radiotherapy/chemotherapy if malignant

Mediastinitis

- most common causes of mediastinitis are postoperative complications of cardiovascular or thoracic surgical procedures

Acute

- etiology
 - complication of endoscopy (e.g. esophageal perforation providing entry point for infection)
 - esophageal or cardiac surgery
 - tumour necrosis
- signs and symptoms
 - fever, substernal pain
 - pneumomediastinum, mediastinal compression
 - Hamman's sign (auscultatory “crunch” during cardiac systole)
- treatment
 - antibiotics, drainage, \pm surgical closure of perforation

Chronic

- usually a granulomatous process or previous infection (e.g. histoplasmosis, TB, sarcoidosis, syphilis)



Pleural Effusions

Definition

- excess amount of fluid in the pleural space (normally up to 25 ml)

Etiology

- disruption of normal equilibrium between pleural fluid formation/entry and pleural fluid absorption/exit
- pleural effusions are classified as transudative or exudative – distinguish clinically using Light's Criteria (Table 21)

Table 21. Laboratory Values in Transudative and Exudative Pleural Effusion ("Light's Criteria")

	Transudate	Exudate
Protein – pleural/serum	<0.5	>0.5
LDH – pleural/serum	<0.6	>0.6
Pleural LDH	<2/3 upper limit of N serum LDH	>2/3 upper limit of N serum LDH

Light RW, Macgregor MI, Luchsinger PC et al. *Ann Intern Med* 1979; 77(4):507-513



Transudative effusions are usually bilateral, not unilateral

Exudative effusions can be bilateral or unilateral



All criteria for transudate must be fulfilled to be considered a transudative effusion. If any one of the criteria for exudates is met – it is an exudate.

Light's Criteria: Sensitivity and Specificity Comparative Analysis of the Biochemical Parameters Used to Distinguish between Pleural Transudates and Exudates.

Chest 1995; 107(6):1604-9

Study: Pleural fluid and medical records for 500 patients were analyzed and the diagnostic accuracy's of the Light's Criteria was assessed. The Light's criteria was compared to other biochemical methods.

Results: Sensitivity: 98%, Specificity: 83%, for identifying exudative pleural effusions.

Comparative Analysis of Light's Criteria and other Biochemical Parameters for Distinguishing Transudates from Exudates.

Respirology Medicine 1998; 92(5):762-765.

Study: Pleural fluid and medical records for 241 patients were assessed and the accuracy of the Light's Criteria for detecting exudative pleural effusions was analyzed. The results were compared to other potential methods for distinguishing between exudative and transudative pleural effusions.

Results: Sensitivity: 97%, Specificity: 71% for identifying exudative pleural effusions.

Transudative Pleural Effusions

- pathophysiology: alteration of systemic factors that affect the formation and absorption of pleural fluid (e.g. increased capillary hydrostatic pressure, decreased plasma oncotic pressure)
- etiology
 - CHF – usually right-sided or bilateral
 - cirrhosis
 - nephrotic syndrome
 - pulmonary embolism (may cause transudative but more often causes exudative effusion)
 - peritoneal dialysis, hypothyroidism, CF, urinothorax

Exudative Pleural Effusions

- pathophysiology: increased permeability of pleural capillaries or lymphatic dysfunction
- etiology
 - infectious
 - ♦ parapneumonic effusion (associated with bacterial pneumonia, lung abscess)
 - ♦ empyema (bacterial, fungal, TB), TB pleuritis, viral infection
 - malignancy
 - ♦ lung carcinoma (35%)
 - ♦ lymphoma (10%)
 - ♦ metastases: breast (25%), ovary, kidney
 - ♦ mesothelioma
 - inflammatory
 - ♦ collagen vascular diseases: RA, SLE
 - ♦ pulmonary embolism, after coronary artery bypass surgery
 - intra-abdominal
 - ♦ subphrenic abscess
 - ♦ esophageal perforation (elevated pleural fluid amylase)
 - ♦ pancreatic disease (elevated pleural fluid amylase)
 - ♦ Meigs' syndrome (ascites and hydrothorax associated with an ovarian fibroma or other pelvic tumour)
 - trauma
 - ♦ chylothorax: occurs when the thoracic duct is disrupted and chyle accumulates in the pleural space, due to trauma, tumour
 - ♦ hemothorax: due to rupture of a blood vessel, commonly by trauma or tumours
 - other
 - ♦ pneumothorax (spontaneous, traumatic, tension)

Signs and Symptoms

- often asymptomatic
- dyspnea: varies with size of effusion and underlying lung function
- pleuritic chest pain
- inspection: trachea deviates away from effusion, ipsilateral decreased expansion
- percussion: decreased tactile fremitus, dullness
- auscultation: decreased breath sounds, bronchial breathing and egophony at upper level, pleural friction rub

Investigations

- CXR
 - must have >200 ml of pleural fluid for visualization on PA film
 - lateral: >50 ml leads to blunting of posterior costophrenic angle
 - PA: blunting of lateral costophrenic angle
 - dense opacification of lung fields with concave meniscus
 - decubitus: fluid will shift unless it is loculated
 - supine: fluid will appear as general haziness
- thoracentesis: indicated if pleural effusion is a new finding
 - risk of re-expansion pulmonary edema if >1.5 L of fluid is removed
 - inspect for colour, character, and odour of fluid
 - analyze fluid (see Tables 21 and 22)
- pleural biopsy: indicated if suspect TB, mesothelioma, or other malignancy (and if cytology negative)
- \pm U/S: detects small effusions and can guide thoracentesis
- treatment depends on cause, \pm drainage if symptomatic
- CT can be helpful in differentiating parenchymal from pleural abnormalities

Table 22. Analysis of Pleural Effusion

Measure	Purpose
Protein, LDH	Transudate vs. exudate (see Table 21)
Gram stain, Ziehl-Nielsen stain (TB), culture	Looking for specific organisms
Cell count differential	Neutrophils vs. lymphocytes (lymphocytic effusion in TB, cancer, lymphoma, serositis)
Cytology	Malignancy, infection
Glucose (low)	RA, TB, empyema, malignancy, esophageal rupture
Rheumatoid factor, ANA, complement	Collagen vascular disease
Amylase	Pancreatitis, esophageal perforation, malignancy
pH	Empyema <7.2, TB and mesothelioma <7.3
Blood	Mostly traumatic, malignancy, PE with infarction, TB
Triglycerides	Chylothorax from thoracic duct leakage, mostly due to trauma, lung CA, or lymphoma

Treatment

- thoracentesis
- treat underlying cause

Complicated Effusion

- persistent bacteria in the pleural space, but fluid is non-purulent
- neutrophils, pleural fluid acidosis, and high LDH
- often no bacteria grown, since rapidly cleared from pleural space
- fibrin layer leading to loculation of pleural fluid
- treatment: antibiotics and drainage, treat as an empyema

Empyema

Definition

- pus in pleural space or an effusion with organisms seen on a Gram stain or culture (i.e. pleural fluid is grossly purulent)
- positive culture is not required for diagnosis

Etiology

- contiguous spread from lung infection (most commonly anaerobes), or infection through chest wall (e.g. trauma, surgery)

Signs and Symptoms

- fever, pleuritic chest pain

Investigations

- CT chest
- thoracentesis
- PMNs (lymphocytes in TB) \pm visible organisms on Gram stain

Treatment

- antibiotic therapy for at least 4-6 weeks (rarely effective alone)
- complete pleural drainage with chest tube
- if loculated, more difficult to drain – may require surgical drainage



Appearance of Pleural Fluid

Bloody – trauma, malignancy
 White – chylothorax, empyema
 Black – aspergillosis, amoebic liver abscess
 Yellow-green – rheumatoid pleurisy
 Viscous – malignant mesothelioma
 Ammonia odour – urinothorax
 Food particles – esophageal rupture



Role of CT in Pleural Effusion

- To assess for fluid loculation, pleural thickening and nodules, parenchymal abnormalities and adenopathy
- Helps to distinguish benign from malignant effusion and transudative from exudative effusion
- May not distinguish empyema from parapneumonic effusion

Features of Malignant Effusion

- Multiple pleural nodules
- Nodular pleural thickening

Features of Exudative Effusion

- Loculation
- Pleural thickening
- Pleural nodules
- Extrapleural fat of increased density



Pleural Effusions

Simple Effusion

pH >7.2, LDH <1/2 serum, glucose >2.2.

Complicated Effusion

pH <7.2, LDH >1/2 serum, glucose <2.2, positive Gram stain. Needs drainage.



When possible, organism-directed therapy, guided by culture sensitivities or local patterns of drug resistance should be utilized.


Need to Rule Out Life-Threatening Tension Pneumothorax

If pneumothorax with:

- Severe respiratory distress
- Tracheal deviation to contralateral side
- Distended neck veins (↑ JVP)
- Hypotension

Do not perform CXR.

Needs immediate treatment.
See Emergency Medicine, ER11

Pneumothorax

Definition

- presence of air in the pleural space

Pathophysiology

- increased intrapleural pressure reduces lung inflation

Etiology

- traumatic – penetrating or non-penetrating chest injuries
- iatrogenic (central venous catheter, thoracentesis, mechanical ventilation with barotrauma)
- spontaneous (no history of trauma)
 - primary (no underlying lung disease)
 - ♦ spontaneous rupture of apical subpleural bleb of lung into pleural space
 - ♦ predominantly tall, healthy, young males
 - secondary (underlying lung disease)
 - ♦ rupture of subpleural bleb which migrates along bronchioalveolar sheath to the mediastinum then to the intrapleural space
 - ♦ necrosis of lung tissue adjacent to pleural surface (e.g. pneumonia, abscess, PCP, lung CA, emphysema)

Signs and Symptoms

- can be asymptomatic
- acute-onset pleuritic chest pain, dyspnea
- tachypnea, tachycardia
- tracheal deviation (contralateral deviation in tension pneumothorax)
- ipsilateral diminished chest expansion
- decreased tactile/vocal fremitus
- hyperresonant percussion note
- ipsilateral diminished breath sounds

Investigations

- CXR
 - small: separation of visceral and parietal pleura seen as fine crescentic line parallel to chest wall at apex
 - large: increased density and decreased volume of lung on side of pneumothorax
 - see Diagnostic Medical Imaging, DM8

Treatment

- small pneumothoraces (<20% with no signs of respiratory/circulatory collapse) resolve spontaneously; breathing 100% oxygen accelerates resorption of air
- small intercostal tube with Heimlich valve for most spontaneous pneumothoraces
- large pneumothoraces or those complicating underlying lung disease require placement of a chest tube connected to underwater seal ± suction
- for repeated episodes: pleurodesis with sclerosing agent or apical bullectomy and abrasion
- treat underlying cause (e.g. antibiotic for PCP)

Asbestos-Related Pleural Disease and Mesothelioma

Etiology and Pathophysiology

- benign manifestations of asbestos exposure
 - “benign asbestos pleural effusion”
 - ♦ exudative effusion, typically ~10 years after exposure, resolves
 - pleural plaques, usually calcified
 - ♦ marker of exposure; usually an asymptomatic radiologic finding
- mesothelioma
 - primary malignancy of the pleura
 - decades after asbestos exposure (even light exposure)
 - smoking not a risk factor, but asbestos and smoking synergistically increase risk of lung cancer

Signs and Symptoms

- persistent chest pain, dyspnea, cough, bloody pleural effusion, weight loss

Investigations

- biopsy (pleuroscopic or open)
- needle biopsy may seed needle tract with tumour

Treatment

- resection (extrapleural pneumonectomy) requires careful patient selection; rarely successful (average survival <1 year)

Pulmonary Edema

- see [Cardiology and Cardiovascular Surgery](#), C34

Respiratory Failure

**Definition**

- to impairment of gas exchange between ambient air and circulating blood
- hypoxemic ($\text{PaO}_2 < 60 \text{ mmHg}$)
- hypercapnic ($\text{PaCO}_2 > 50 \text{ mmHg}$)
- acute vs. chronic (compensatory mechanisms activated)

Classification

- airway obstruction: COPD, bronchiectasis, CF, asthma, bronchiolitis, upper airway obstruction
- abnormal parenchyma: pneumonia, pulmonary edema, pulmonary fibrosis, acute respiratory distress syndrome (ARDS), pleural effusion
- hypoventilation without bronchopulmonary disease: CNS disorder (drugs, increased ICP, spinal cord lesion, sepsis), neuromuscular (myasthenia gravis, Guillain-Barré, muscular dystrophies), chest wall (kyphoscoliosis, obesity)

Signs and Symptoms

- signs of underlying disease
- hypoxemia: restlessness, confusion, cyanosis, coma, cor pulmonale
- hypercapnia: headache, dyspnea, drowsiness, asterixis, warm periphery, plethora, increased ICP (secondary to vasodilatation)

Investigations

- serial ABGs
- CXR and/or CT, bronchoscopy to characterize underlying cause if unclear

Hypoxemic Respiratory Failure

Definition

- PaO_2 decreased, PaCO_2 normal or decreased

Pathophysiology

- low inspired FiO_2 (e.g. high altitude)
- normal FiO_2
 - diffusion impairment: interstitial lung disease
 - V/Q mismatch: airway disease (asthma, COPD), alveolar disease (pneumonia, edema), vascular disease (PE)
 - shunts: alveolar collapse, intra-alveolar filling (pneumonia, edema), intracardiac (R to L), intrapulmonary (AVM)
 - low mixed venous saturation: anemia, low cardiac output, hypermetabolism

Treatment

- reverse the underlying pathology
- maintain oxygenation
- enrichment of FiO_2 (if shunt present, supplemental O_2 is less effective)
- positive pressure: use of PEEP/CPAP can recruit alveoli and redistribute lung fluid
- \pm hemodynamic support: fluids, vasopressors, inotropes, reduction of O_2 requirements

**Causes of Hypoxemia**

1. Low FiO_2
2. Hypoventilation
3. Shunting
4. Low mixed venous O_2 content
5. V/Q mismatch

Table 23. Approach to Hypoxemia

Type of Hypoxemia	Settings	PaCO ₂	A-aDO ₂	Oxygen Therapy	Ventilation, BiPAP and PEEP	Improved Cardiac Output
1. Low FiO ₂	Postop, high altitude	Normal, Low	Normal	Improves	No change	No change
2. Hypoventilation	Drug overdose	High	Normal	Improves	Improves with ventilation	No change
3a. Shunt	ARDS, Pneumonia	Low, Normal	Increased	No change	Improves (except if one-sided)	Improves
3b. Shunt (Right to Left)	Pulmonary HTN	Normal, Low	Increased	No change	Worsens	Worsens
4. Low mixed venous O ₂ content	Shock	Low	Increased	No change	Worsens	Improves
5. V/Q mismatch	COPD	High, Normal	Increased	Improves with small amounts	Often improves	Improves

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Hypercapnic Respiratory Failure

- PaCO₂ increased, PaO₂ decreased

Pathophysiology

- increased CO₂ production: fever, sepsis, seizure, acidosis, carbohydrate load
- alveolar hypoventilation: COPD, asthma, CF, chest wall disorder, rapid shallow breathing
- hypoventilation
 - central: brainstem stroke, hypothyroidism, severe metabolic alkalosis, drugs (opiates, benzodiazepines)
 - neuromuscular: myasthenia gravis, Guillain-Barré, phrenic nerve injury, muscular dystrophy, polymyositis, kyphoscoliosis
 - muscle fatigue

Treatment

- reverse the underlying pathology
- if PaCO₂ >50 mmHg and pH is acidemic consider noninvasive or mechanical ventilation
- correct exacerbating factors
 - NTT/ETT suction: clearance of secretions
 - bronchodilators: reduction of airway resistance
 - antibiotics: treatment of infections
- maintain oxygenation (see above)
- diet: increased carbohydrate can increase PaCO₂ in those with mechanical or limited alveolar ventilation; high lipids decrease PaCO₂

Acute Respiratory Distress Syndrome (ARDS)

- clinical syndrome characterized by severe respiratory distress, hypoxemia, and noncardiogenic pulmonary edema
- American-European Consensus Conference (1994) criteria for ARDS:
 1. acute onset
 2. bilateral infiltrates on CXR
 3. PCWP ≤18 or no evidence of increased left atrial pressure
 4. PaO₂/FiO₂ ≤200

Etiology

- may result from direct or indirect lung injury:
 - airway: aspiration (gastric contents, drowning), pneumonia, gas inhalation (oxygen toxicity, nitrogen dioxide, smoke)
 - circulation: sepsis, shock, trauma, pancreatitis, DIC, blood transfusion, embolism (fat, amniotic fluid), drug overdose (narcotics, sedatives, TCAs)
 - neurogenic: head trauma, intracranial hemorrhage

Pathophysiology

- disruption of alveolar capillary membranes → leaky capillaries → interstitial and alveolar pulmonary edema → reduced compliance, V/Q mismatch, shunt, hypoxemia, pulmonary HTN



Causes of Hypercapnia

1. High Inspired CO₂
2. Low Total Ventilation
3. High Dead-space Ventilation
4. High CO₂ Production



In chronic hypercapnia, supplemental O₂ may decrease the hypoxic drive to breathe, but do not deny oxygen if the patient is hypoxic.



In COPD patients with chronic hypercapnia ("CO₂ retainers"), provide supplemental oxygen to achieve target SaO₂ from 88-92%.

Clinical Course

A. Exudative Phase

- first 7 days of illness after exposure to ARDS precipitant
- alveolar capillary endothelial cells and type I pneumocytes are injured, resulting in loss of normally tight alveolar barrier
- patients develop dyspnea, tachypnea, increased work of breathing
 - these result in respiratory fatigue and eventually respiratory failure (see *Hypoxemic Respiratory Failure*, R25)

B. Proliferative Phase

- day 7-21
- may still experience dyspnea, tachypnea, fatigue, and hypoxemia
- some patients develop fibrotic lung changes
- most patients clinically improve and are able to wean off mechanical ventilation

C. Fibrotic Phase

- some patients will enter a fibrotic phase that may require long-term support on supplemental oxygen or even mechanical ventilation
- if fibrosis present, associated with increased mortality

Treatment

- based on ARDS network (see *Landmark Respirology Trials*, R38)
- treat underlying disorder (e.g. antibiotics if infection present)
- mechanical ventilation using low tidal volumes (<6 ml/kg) to prevent barotrauma
 - use optimal amount of PEEP (positive end-expiratory pressure) to keep airways open and allow the use of lower FiO₂
 - may consider using prone ventilation, and/or inhaled nitric oxide, high frequency oscillator or ECMO (extracorporeal membrane oxygenation) if conventional treatment is failing
- fluids and inotropic therapy (e.g. dopamine, vasopressin) if cardiac output inadequate
- pulmonary-arterial catheter now seldom used for monitoring hemodynamics
- mortality: 30-40%, usually due to non-pulmonary complications
- sequelae of ARDS include residual pulmonary impairment, severe debilitation, polyneuropathy and psychologic difficulties, which gradually improve over time
- most survivors eventually regain near-normal lung function, often with mildly reduced diffusion capacity

Mechanical Ventilation

- see *Anesthesia*, A10

Definition

- artificial means of supporting ventilation and oxygenation
- mechanically ventilated patients may require some sedation and/or analgesia

Indications

- general indications
 - hypoxemic respiratory failure
 - hypercapnic respiratory failure
- specific indicators for mechanical ventilation
 - acute ventilation failure/acute respiratory acidosis
 - refractory hypoxemia
 - reduced level of consciousness
 - facilitation of surgical procedures

Ventilator Strategies

- target tidal volume, respiratory rate, PEEP and ratio of inspiratory to expiratory time are all determined based on the underlying reason for mechanical ventilation
- hypoxemic respiratory failure: ventilator provides supplemental oxygen and helps improve V/Q mismatch and decreases intrapulmonary shunt
- hypercapnic respiratory failure: ventilator augments alveolar ventilation; may decrease the work of breathing, allowing respiratory muscles to rest

Modes of Ventilation

- assist-control ventilation (ACV) (often initial mode of ventilation)
 - every breath is delivered with a pre-set tidal volume
 - inspiration may be triggered by patient effort; if no effort is detected within a specified amount of time the ventilator will initiate the breath



Tracheostomy

- Tracheostomy should be considered in patients who require ventilator support for extended periods of time
- Shown to improve patient comfort and give patients a better ability to participate in rehabilitation activities



Positive End Expiratory Pressure (PEEP)

- Positive pressure applied at the end of ventilation which opens up collapsed alveoli decreasing V/Q mismatch
- Used with all invasive modes of ventilation



Monitoring Ventilatory Therapy

- Pulse oximetry, end-tidal CO₂ concentration
- Regular arterial blood gases
- Assess tolerance regularly



- Management of pneumothorax in patients on mechanical ventilation → chest tube.

- synchronous intermittent mandatory ventilation (SIMV)
 - ventilator provides breaths at fixed rate and tidal volume
 - patient can breathe spontaneously between ventilator breaths
 - PEEP is still applied and therefore spontaneous breaths still supported
- pressure support ventilation (PSV)
 - patient initiates all breaths and the ventilator supports each breath with a pre-set inspiratory pressure
 - useful for weaning off ventilator
- pressure control ventilation (PCV)
 - a minimum frequency is set and patient may trigger additional breaths above the ventilator
 - all breaths delivered at a preset constant inspiratory pressure
- noninvasive ventilation (NIV)
 - achieved without intubation by using a nasal mask with:
 - ♦ BiPAP (bilevel positive airway pressure): a wave of increased pressure on inspiration and lower constant pressure on expiration
 - ♦ CPAP (continuous positive airway pressure): constant pressure

Complications of Mechanical Ventilation

- barotrauma
 - pneumothorax, tension pneumothorax, pneumomediastinum, subcutaneous emphysema, ventilator-induced lung injury (from the use of high tidal volumes – can resemble ARDS)
- ventilator associated pneumonia (nosocomial pneumonia)
 - patients intubated 72 hours are at high risk of acquiring pneumonia
 - common organisms include enteric Gram-negative rods, anaerobes, *S. aureus*
- hypotension (decreased CO)
 - increased intrathoracic pressure with decreased venous return that usually responds to intravascular volume repletion
- stress ulcers
 - may be prevented with H₂-blocker prophylaxis
- tracheal stenosis
- laryngeal dysfunction



Neoplasms

Approach to the Solitary Pulmonary Nodule

- also see [Diagnostic Medical Imaging](#), DM7

Definition

- a round or oval, sharply circumscribed radiographic lesion up to 3-4 cm, which may or may not be calcified, and is surrounded by normal lung
- can be benign or malignant

Table 24. Differential Diagnosis for Benign vs. Malignant Solitary Nodule

Benign (70%)	Malignant (30%)
Infectious granuloma (histoplasmosis, coccidiomycosis, TB, atypical mycobacteria)	Bronchogenic carcinoma
Other infections (bacterial abscess, PCP, aspergilloma)	Adenocarcinoma
Benign neoplasms (hamartoma, lipoma, fibroma)	Squamous cell carcinoma
Vascular (AV malformation, pulmonary varix)	Large cell carcinoma
Developmental (bronchogenic cyst)	Small cell carcinoma
Inflammatory (Wegener's granulomatosis, rheumatoid nodule, sarcoidosis)	Metastatic lesions
Other (hematoma, infarct, pseudotumour, rounded atelectasis, lymph nodes, amyloidoma)	Breast
	Head and neck
	Melanoma
	Colon
	Kidney
	Sarcoma
	Germ cell tumours
	Pulmonary carcinoid

Investigations (see Figure 11)

- CXR: always compare with previous CXR (see Table 25)
- CT densitometry and contrast enhanced CT of thorax
- sputum cytology: usually poor yield
- biopsy (bronchoscopic or percutaneous) or excision (thoracoscopy or thoracotomy): if clinical and radiographic features do not help distinguish between benign or malignant lesion
 - if at risk for lung cancer, biopsy may be performed regardless of radiographic features
 - if a biopsy is non-diagnostic, whether to observe, re-biopsy or resect will depend on the level of suspicion
- watchful waiting: repeat CXR and/or CT scan at 3, 6, 12 months
- PET scan not yet routine but can help distinguish benign from malignant nodules



Pulmonary neoplasms may present as a solitary pulmonary nodule identified incidentally on a radiographic study (~10% of cases) or as symptomatic disease (most cases).



Corona Radiata Sign on Chest CT

- Fine striations that extend linearly from a nodule in a spiculated fashion
- Highly associated with malignancy

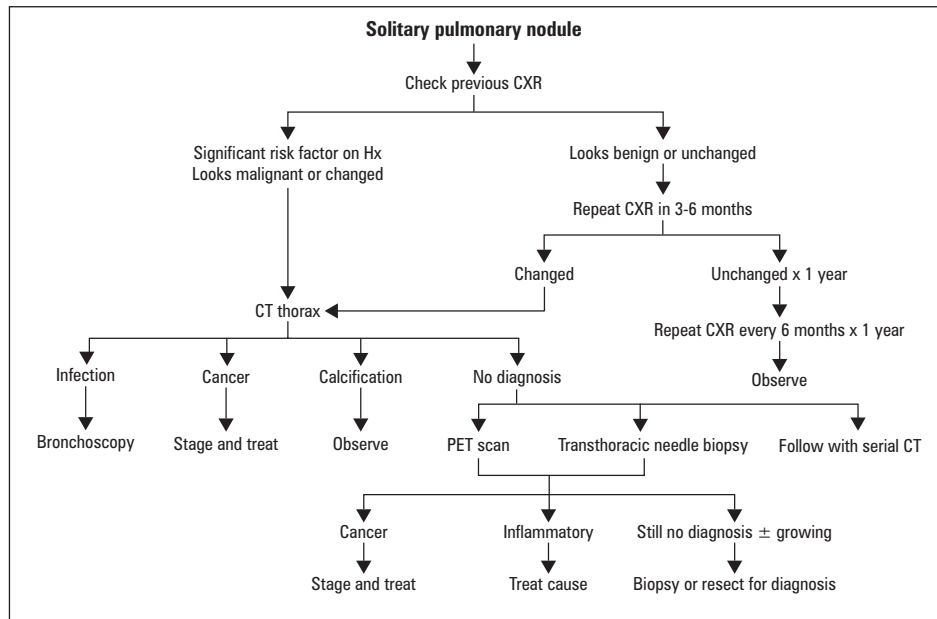


Terminology

"nodule" <3 cm
"mass" >3 cm

Table 25. CXR Characteristics of Benign vs. Malignant Solitary Nodule

Parameters	Benign	Malignant
Size	<3 cm, round, regular	>3 cm, irregular, spiculated
Margins	Smooth margin	Ill-defined or notched margin
Features	Calcified pattern: central, "popcorn" pattern if hamartoma, usually no cavitation; if cavitated, wall is smooth and thin, no other lung pathology	Usually not calcified; if calcified, pattern is eccentric, no satellite lesions, cavitation with thick wall, may have pleural effusions, lymphadenopathy
Doubling Time	Doubles in <1 month or >2 years	Doubles in >1 month or <2 years

**Figure 11. Evaluation of a Solitary Pulmonary Nodule**

Benign Lung Tumours

Epidemiology

- less than 5% of all primary lung neoplasms
- bronchial adenomas and hamartomas comprise 90% of the benign neoplasms of the lung
- uncommon benign neoplasms of the lung include fibromas, lipomas, leiomyomas, hemangiomas, papillomas, chondromas, teratoma and endometriosis

Signs and Symptoms

- cough, hemoptysis, recurrent pneumonia, wheezing, atelectasis
- can present as an asymptomatic solitary pulmonary nodule (see previous section)

Classification

- bronchial adenomas
 - slow-growing, low-grade endobronchial tumours that rarely metastasize
 - may be carcinoids (90%), adenocystic tumours, or mucoepidermoid
 - symptoms
 - ♦ systemic symptoms usually absent
 - ♦ patients may complain of chronic cough, wheezing or give a history of recurrent pneumonia
 - ♦ hemoptysis may be present
- bronchial carcinoids
 - often in young adults; smoking not a risk factor
 - clinical presentation: follows a slow course, metastasizes late
 - carcinoid syndrome (flushing, diarrhea, cardiac valvular lesions, wheezing) is rarely associated with pulmonary carcinoids
 - may cause paraneoplastic syndromes (see Table 27)
 - treatment and prognosis: amenable to resection; 5-year survival is 95%
 - atypical carcinoid: more aggressive form, tends to metastasize
- hamartomas
 - composed of tissues normally present in lung (fat, epithelium, fibrous tissue and cartilage), but they exhibit disorganized growth
 - peak incidence at age 60, more common in men, 10% of benign lung lesions [2nd to infectious granuloma (80%)]
 - usually peripheral, clinically silent, and benign in behaviour
 - CXR: clustered "popcorn" pattern of calcification is pathognomonic for hamartoma



Malignant lung tumours are the most common cause of cancer mortality throughout the world in both men and women.

Malignant Lung Tumours

Pathological Classification

- bronchogenic cancer (90% of primary lung cancers, see Table 26)
 - classified into small cell lung cancer (SCLC) and non-SCLC (NSCLC, e.g. adenocarcinoma, squamous cell, large cell), bronchioalveolar cancer (BAC)
 - incidence of adenocarcinoma is increasing
- lymphoma
- secondary metastases: breast, colon, prostate, kidney, thyroid, stomach, cervix, rectum, testes, bone, melanoma

Table 26. Characteristics of Bronchogenic Cancer

Cell Type	Incidence	Correlation with smoking	Location	Histology	Metastasis
Adenocarcinoma	M: 35% F: 40%	Weak	Peripheral	Glandular, mucin producing	Early, distant
Squamous cell carcinoma (SCC)	30%	Strong	Central	Keratin, intercellular bridges	Local invasion and distant spread, may cavitate
SCLC	25%	Strong	Central	Oat cell, neuroendocrine	Disseminated at presentation Origin in endobronchial cells
Large cell carcinoma	10-15%	Strong	Peripheral	Anaplastic, undifferentiated	Early, distant

Epidemiology

- most common non-skin cancer in men and women
- most common cause of cancer death in men and women
- 18% of all cancer related deaths

Risk Factors

- cigarette smoking: 85% of lung cancer related to smoking
- asbestos 5x increased risk, asbestos + smoker 80-90x increased risk
- radiation: radon, uranium (especially if smoker)
- arsenic, chromium, nickel exposure
- genetic damage
- parenchymal scarring: granulomatous disease, fibrosis, scleroderma
- passive exposure to cigarette smoke
- air pollution: exact role is uncertain
- HIV

Signs and Symptoms

- cough (75%): beware of chronic cough that changes in character
- dyspnea (60%)
- chest pain (45%)
- hemoptysis (35%)
- other pain (25%)
- clubbing (21%)
- constitutional symptoms: anorexia, weight loss, fever, anemia

Presentation by Location of Tumour Extension

- lung, hilum, mediastinum, pleura: pleural effusion, atelectasis, wheezing
- pericardium: pericarditis, pericardial tamponade
- esophageal compression: dysphagia
- phrenic nerve: paralyzed diaphragm
- recurrent laryngeal nerve: hoarseness
- superior vena cava syndrome:
 - obstruction of SVC causing neck and facial swelling, as well as dyspnea and cough
 - other symptoms: hoarseness, tongue swelling, epistaxis, and hemoptysis
 - physical findings: dilated neck veins, increased number of collateral veins covering the anterior chest wall, cyanosis, edema of the face, arms, and chest, Pemberton's sign
 - milder symptoms if obstruction is above the azygos vein
- lung apex (Pancoast tumour): Horner's syndrome, brachial plexus palsy (most commonly C8 and T1 nerve roots)
- rib and vertebrae: erosion
- distant metastasis to brain, bone, liver, adrenals
- paraneoplastic syndromes (see Table 27)
 - a group of disorders associated with malignant disease, not related to the physical effects of the tumour itself
 - most often associated with SCLC



Horner has a MAP of the Coast
A Pancoast tumour compresses the cervical sympathetic plexus causing a Horner's syndrome:
Miosis
Anhidrosis
Ptosis

Table 27. Paraneoplastic Syndromes

System	Clinical Presentation	Associated Malignancy
Skeletal	Clubbing, hypertrophic pulmonary osteoarthropathy (HPOA)	NSCLC
Dermatologic	Acanthosis nigricans Dermatomyositis	Bronchogenic cancer Bronchogenic cancer
Endocrine	Hypercalcemia (osteolysis or PTHrP) Hypophosphatemia Hypoglycemia Cushing's syndrome (ACTH) Somatostatinoma syndrome SIADH	Squamous cell cancer Squamous cell cancer Sarcoma SCLC Bronchial carcinoid SCLC
Neuromyopathic	Lambert-Eaton syndrome Polymyositis Subacute cerebellar degeneration Spinocerebellar degeneration Peripheral neuropathy	SCLC
Vascular/Hematologic	Nonbacterial endocarditis Trousseau's syndrome (migratory thrombophlebitis) DIC	Bronchogenic cancer NSCLC
Renal	Nephrotic syndrome	



2/3 of primary lung cancer is found in the upper lung; 2/3 of metastases occur in the lower lung (hematogenous spread secondary to increased blood flow to the base of the lung).

Investigations

- initial diagnosis
 - imaging: CXR, CT chest + upper abdomen, PET scan, bone scan
 - cytology: sputum
 - biopsy: bronchoscopy, percutaneous, mediastinoscopy
- staging work-up
 - blood work: electrolytes, LFTs, calcium, ALP
 - imaging: CXR, CT thorax and upper abdomen, bone scan, neuroimaging
 - invasive: bronchoscopy, mediastinoscopy, mediastinotomy, thoracotomy

Staging/Treatment

Table 28. SCLC vs. NSCLC

	Stage	Definition	Treatment	Median Survival
SCLC	Limited stage	Confined to single radiation port	Radiation ± chemo	1-2 years
	Extensive stage	(one hemithorax and regional lymph nodes) Extension beyond a single radiation port	± prophylactic to brain Chemotherapy	6 months
	Stage (TNM ISS)		Treatment	5 Year Survival
NSCLC	I	No invasion beyond lung and nodes negative	Surgery	~50%
	II	No invasion beyond lung and ipsilateral hilar Nodes positive	Surgery + radiation	30%
	IIIA	Direct extension to chest wall, pleura, pericardium or ipsilateral mediastinal nodes positive	Chemotherapy + radiation followed by surgery	15%
	IIIB	Advanced local involvement (malignant effusion, major structures), or contralateral nodes positive	Radiation ± chemo ± surgery	5%
	IV	Distant metastasis	Palliative	<2%

Therapy for Bronchogenic Cancer

- surgery
 - surgery not usually performed since SCLC is generally non-curable
 - preferred treatment of stage I and II NSCLC is resection with a curative intent
 - advanced NSCLC (stage III and IV) is often palliated with chemotherapy and/or radiation
 - contraindications:
 - spread to contralateral lymph nodes or distant sites
 - patients with surgically resectable disease must undergo mediastinal node sampling since CT thorax is not accurate in 20-40% of cases
 - poor pulmonary status (e.g. unable to tolerate resection of lung)
 - perioperative mortality
 - 6% if pneumonectomy
 - 3% if lobectomy
 - 1% if segmentectomy
- chemotherapy (no role for chemo alone, only in combination with other treatments)
 - cisplatin and etoposide
 - paclitaxel, vinorelbine, and gemcitabine are newer NSCLC therapies
 - new biologics, e.g. epidermal growth factor inhibitor (Gefitinib)



Combination treatment may be superior, giving better response rates.

- complications:
 - ♦ acute: tumour lysis syndrome, infection, bleeding, myelosuppression, hemorrhagic cystitis (cyclophosphamide), cardiotoxicity (doxorubicin), renal toxicity (cisplatin), peripheral neuropathy (vincristine)
 - ♦ chronic: neurologic damage, leukemia, additional primary neoplasms
- radiotherapy
- palliative care for end-stage disease

Prognosis of Bronchogenic Cancer

- 5 year survival rates for different subtypes:
 - squamous cell carcinoma 25%
 - adenocarcinoma 12%
 - large cell carcinoma 13%
 - SCLC 1% (poorest prognosis)
 - NSCLC (see Table 28)
- greatest tendency to metastasize
- 70% present with extensive disseminated disease at initial diagnosis
- limited-stage: 15-20% cure rate
- extensive-stage treated: median survival of 6 months, but can live up to two years with a rare cure (1%); untreated median survival is 2-3 months

BRONCHOALVEOLAR CARCINOMA

- a type of adenocarcinoma that grows along the alveolar wall in the periphery
- may arise at sites of previous lung scarring
- clinical presentation: similar to bronchogenic cancer; late metastasis
- treatment and prognosis: solitary lesions are resectable with a 60% 5-year survival rate; overall survival rate is 25%

Sleep-Related Breathing Disorders

- normal changes during sleep: tidal volume decreases, arterial CO₂ increases (due to decreased minute ventilation), pharyngeal dilator muscles relax causing increased upper airway resistance
- sleep-related breathing disorders: a group of disorders characterized by decreased air-flow occurring only in sleep or worsening in sleep
- affects 9% of men, 4% of women
- sleep apnea
- hypoventilation syndromes
 - primary alveolar hypoventilation: idiopathic
 - obesity-hypoventilation syndrome (Pickwickian syndrome)
 - respiratory neuromuscular disorders

Sleep Apnea

Definition

- episodic decreases in airflow during sleep
- quantitatively measured by the Apnea/Hypopnea Index (AHI) = # of apneic and hypopneic events per hour of sleep
- sleep apnea generally accepted to be present if AHI >15

Classification

- obstructive (OSA)
 - caused by transient, episodic obstruction of the upper airway
 - absent or reduced airflow despite persistent respiratory effort
- central (CSA)
 - caused by transient, episodic decreases in CNS drive to breathe
 - no airflow because no respiratory effort
 - Cheyne-Stokes Respiration (CSR): a form of CSA in which central apneas alternate with hyperpneas to produce a crescendo-decrescendo pattern of tidal volume; seen in severe LV dysfunction, brain injury, and other settings (Figure 2)
- mixed (MSA)
 - features of both OSA and CSA
 - loss of hypoxic and hypercapnic drives to breathe secondary to “resuscitative breathing”: overcompensatory hyperventilation upon awakening from OSA induced hypoxia



Apneic – no breathing for ≥10 seconds

Hypopneic – >50% reduction in ventilation for ≥10 seconds

Risk Factors

- for OSA: obesity, upper airway abnormality, neuromuscular disease, hypothyroidism, alcohol/sedative use, nasal congestion, sleep deprivation
- for CSA: LV failure, brain-stem lesions, encephalitis, encephalopathy, myxedema, high altitude

Signs and Symptoms

- obtain history from spouse/partner
- secondary to repeated arousals and fragmentation of sleep: daytime somnolence, personality and cognitive changes, snoring
- secondary to hypoxemia and hypercapnia: morning headache, polycythemia, pulmonary/systemic HTN, cor pulmonale/CHF, nocturnal angina, arrhythmias
- OSA typically presents in a middle-aged obese male snorer
- CSA can be due to neurological disease

Investigations

- sleep study (polysomnography)
 - evaluates sleep stages, airflow, ribcage movement, ECG, SaO₂, limb movements
 - indications
 - ♦ excessive daytime sleepiness
 - ♦ unexplained pulmonary HTN or polycythemia
 - ♦ daytime hypercapnia
 - ♦ titration of optimal nasal CPAP
 - ♦ assessment of objective response to other interventions

Treatment

- modifiable factors: weight loss, decreased alcohol/sedatives, nasal decongestion, treatment of underlying medical conditions
- OSA or MSA: nasal CPAP, postural therapy (i.e. no supine sleeping), dental appliance, uvulopalatopharyngoplasty, tonsillectomy
- CSA or hypoventilation syndromes: nasal BiPAP/CPAP, respiratory stimulants (e.g. progesterone) in select cases
- tracheostomy rarely required and should be used as last resort for OSA

Complications

- depression, weight gain, decreased quality of life, workplace and vehicular accidents, cardiac complications (e.g. HTN), reduced work/social function

Continuous Positive Airways Pressure for Obstructive Sleep Apnea

The Cochrane Database of Systematic Reviews 2008, Issue 2

Study: Pooled analysis of 36 RCTs (1718 people) comparing nocturnal CPAP with an inactive control or oral appliances in adults with obstructive sleep apnea.

Conclusions: The use of CPAP showed significant improvements in objective and subjective measures including cognitive function, sleepiness, measures of quality of life, and a lower average systolic and diastolic blood pressure. People who responded equally well to CPAP and oral appliances expressed a strong preference for oral appliances; however, participants on oral appliances were more likely to withdraw from therapy.



CPAP has been shown to reduce cardiovascular risk and cardiovascular related deaths in patients with obstructive sleep apnea.

Introduction to Intensive Care

- goal of the intensive care unit (ICU) is to provide stabilization in the setting of an acutely or severely ill patient
- hemodynamic, respiratory or cardiac instability, or widespread infection warrant ICU admission
- ICUs are intended to reverse the abnormal physiology, contain the underlying problem and create a favourable environment for recovery until the patient is stable enough to be transferred
- features unique to ICU are:
 - high nurse to patient ratio
 - extensive invasive cardiopulmonary and other system support monitoring

ICU Basics

Lines and Catheters

- arterial lines
 - used to monitor beat-to-beat blood pressure variations, obtain blood for routine ABGs, common sites are femoral or radial lines
- central venous catheter (central line)
 - used to administer IV fluids, monitor central venous pressure, insert pulmonary artery catheters, give parenteral nutrition, give agents which are too irritating to be given via a peripheral line, when peripheral access is not possible
 - common sites include: internal jugular vein, subclavian vein, femoral vein
- pulmonary arterial catheter
 - uses a balloon "sail" to guide the catheter from a major vein to the right heart
 - "wedged" in the pulmonary artery temporarily to take a variety of measurements
 - rarely used due to associated complications



A catheter "wedged" in the distal pulmonary artery measures pressure transmitted from the pulmonary venous system. This is known as the pulmonary capillary wedge pressure (PCWP). The PCWP reflects left atrial pressure (as long as there is no pulmonary venous disease) and LV diastolic pressure (as long as there is no mitral valve disease). PCWP is high in cardiogenic shock and low in hypovolemic shock.

Source: Cecil Essentials of Medicine, 6th Edition.

- indications:
 - ♦ diagnosis of shock states, primary pulmonary hypertension (PPH), valvular disease, intracardiac shunts, cardiac tamponade, and pulmonary embolism (PE)
 - ♦ assessing hemodynamic response to therapies
 - ♦ differentiation of high- versus low-pressure pulmonary edema
 - ♦ monitoring and management of complicated MI
 - ♦ management of multiorgan system failure and/or severe burns
 - ♦ management of hemodynamic instability after cardiac surgery
- absolute contraindications:
 - ♦ tricuspid or pulmonary valve mechanical prosthesis
 - ♦ right heart mass (thrombus and/or tumour)
 - ♦ tricuspid or pulmonary valve endocarditis

Table 29. Useful Equations and Cardiopulmonary Parameters

Body Surface Area (BSA) = $[\text{Ht (cm)} + \text{Wt (kg)} - 60]/100$

PCWP (Pulmonary Capillary Wedge Pressure) = LVEDP (Left Ventricular End Diastolic Pressure)

Cardiac Index (CI) = Cardiac Output/BSA

Stroke Volume Index (SVI) = CI/Heart Rate

RV Ejection Fraction = SV/RVEDV

Systemic vascular resistance index (SVRI) = $[(\text{MAP} - \text{right atrial pressure (RAP)}) + 80]/\text{CI}$

P:F ratio = $\text{PaO}_2/\text{FiO}_2$

ICU Approach to Management

- the initial assessment of the critically ill patient focuses on life-threatening processes that require immediate diagnostic and/or therapeutic intervention
- management is based on the understanding of the pathophysiology of the disease process taking into consideration organ-system dependence

Organ Failure

- respiratory failure (see *Respiratory Failure*, R25)
- coagulopathy (see *Hematology*, H33)
 - coagulopathies commonly occur in acutely and severely ill patients
 - monitor for:
 - ♦ thrombocytopenia
 - ♦ INR, PTT elevations
 - ♦ DIC (increase in fibrin degradation products and reduction in fibrinogen)
- liver failure (see *Gastroenterology*, G34)
 - manifested by rise in transaminases, bilirubin, INR and hypoglycemia
- renal failure (see *Nephrology*, NP19)
 - damage sustained by hypovolemia, nephrotoxins
 - patients typically develop acute tubular necrosis (ATN)
 - goal of treatment: correct volume and electrolyte status, eliminate toxins
 - common treatment modalities: diuretics, dialysis (early aggressive daily dialysis is key)

Shock

- see *Emergency Medicine*, ER3
- inadequate tissue perfusion potentially resulting in end organ injury
 - categories of shock include
 - ♦ hypovolemic: hemorrhagic, dehydration, vomiting, diarrhea, interstitial fluid redistribution
 - ♦ cardiogenic: myopathic (myocardial ischemia ± infarction), mechanical, arrhythmic, pharmacologic
 - ♦ obstructive: massive PE (saddle embolus), pericardial tamponade, constrictive pericarditis, increased intrathoracic pressure (e.g. tension pneumothorax)
 - ♦ distributive: sepsis, anaphylactic reaction, neurogenic, endocrinologic, toxic

Intensive Insulin Therapy in Critically Ill Patients *NEJM* 2001; 345:1359-67

Study: Prospective, randomized controlled clinical outcome study.

Patients: 1548 patients admitted to the ICU

Intervention: At admission, patients were randomly assigned to either intensive insulin therapy or conventional therapy. Those in the intensive group had an infusion started if BG exceeded 6.1 mmol/L, and maintained to keep BG between 4.4 to 6.1 mmol/L.

Those in the conventional group were started on insulin only if BG exceeded 11.9, and the infusion was adjusted for a target between 10.0 and 11.1 mmol/L.

Primary Outcome: Death from any cause during ICU stay.

Results: 35 patients (4.6%) died in the intensive group in the ICU, versus 63 patients (8.0%) in the conventional group. This represents a 32% mortality reduction ($p=0.04$). Intensive insulin therapy also reduced overall in-hospital mortality, lowered deaths due to sepsis, multi-organ failure. Most of the mortality benefit was seen in long stay patients (>5 days).

Conclusion: Intensive insulin therapy in the ICU reduces mortality by 32%, and improves in-hospital mortality and morbidity.



Shock: Clinical Correlation

Hypovolemic: patients have cool extremities due to peripheral vasoconstriction.

Cardiogenic: patients usually have signs of left-sided heart failure.

Obstructive: varied presentation.

Distributive: patients have warm extremities due to peripheral vasodilation.

Table 30. Changes Seen in Different Classes of Shock

	Hypovolemic	Cardiogenic	Obstructive	Distributive
HR	↑	↑, N, or ↓	↑	↑
BP	↓	↓	↓	↓
JVP	↓	↑	↑	↓
Extremities	Cold	Cold	N or Cold	Warm
Other	Look for visible hemorrhage or signs of dehydration	Bilateral crackles on chest exam	Depending on cause, may see pulsus paradoxus, Kussmaul's sign, or tracheal deviation	Look for obvious signs of infection or anaphylaxis

- treatment should be directed at underlying etiology once it becomes clear
- treatment goal is to return critical organ perfusion to normal (e.g. normalize BP)
- common treatment modalities include:
 - fluid resuscitation
 - inotropes (e.g. dobutamine), vasopressors (e.g. norepinephrine), vasopressin
 - revascularization or thrombolytics for ischemic events

Infection/Sepsis

- the leading cause of death in noncoronary ICU settings is multi-organ failure due to sepsis
- treating sepsis is one of the biggest challenges faced by ICU staff as the underlying pathophysiology of this condition is not fully understood
- the predominant theory is that sepsis is attributable to uncontrollable immune system activation
- formal definitions for sepsis-related terms are as follows:
 - infection: pathologic process caused by the invasion of normally sterile tissue or fluid by pathogenic or potentially pathogenic microorganisms
 - bacteremia: the presence of viable bacteria in the blood
 - **Systemic Inflammatory Response Syndrome (SIRS)**: clinical insults, including both infectious and noninfectious entities that result in a generalized inflammatory reaction manifested by two or more of the following:
 - ♦ body temperature >38.5°C or <35°C
 - ♦ heart rate >90/min
 - ♦ respiratory rate >20/min or PaCO₂ <32 mmHg
 - ♦ WBC >12000 cells/mL or <4000 cells/mL or >10% bands
 - **Sepsis**: clinical syndrome defined by the presence of both infection and SIRS and is classified by severity (see Table 31):
 - ♦ severe sepsis: sepsis associated with organ dysfunction, hypoperfusion or hypotension
 - ♦ septic shock: sepsis with arterial hypotension despite adequate fluid resuscitation
 - ♦ multiorgan dysfunction syndrome: sepsis in the presence of altered organ function such that homeostasis cannot be maintained without intervention

Table 31. Clinical Manifestations of Sepsis

General Variables	Organ dysfunction variables
Fever (>38°C) or Hypothermia (<36°C)	Arterial hypoxemia (PaO ₂ /FiO ₂ <300)
Heart rate >90/min	Acute oliguria (urine output <0.5 mL/kg/hr)
sBP <90 mmHg, MAP <70, or a sBP decrease >40 mmHg	Creatinine increase >0.5 mg/dL
Tachypnea	Coagulation abnormalities (INR >1.5 or aPTT >60 secs)
Altered mental status	Ileus (absent bowel sounds)
Positive fluid balance (>20 mL/kg over 24 hrs)	Thrombocytopenia (platelet count <100,000/L)
Hyperglycemia (BG >7.7 mmol/L) in the absence of diabetes	Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)
Leukopenia (WBC <4,000/L)	Leukocytosis (WBC >12,000/L)
Normal WBC count with >10% immature forms	Tissue perfusion variables
Plasma C-reactive protein >2 SD above the normal value	Hyperlactatemia (>1 mmol/L)
	Decreased capillary refill or mottling

Table adapted with permission from Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent J-L, Ramsay G. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Critical Care Medicine* 2003; 31(4):1250-6

Basic Principles for the Management of Sepsis

- identify the cause and source of infection: blood, sputum, urine Gram stain and C&S
- initiate empiric antibiotic therapy
- monitor, restore and maintain hemodynamic function

Effect of Treatment with Low Doses of Hydrocortisone (HC) and Fludrocortisone (FC) on Mortality in Patients with Septic Shock

JAMA 2002; 288:862-71

Study: Placebo-controlled, randomized, double-blind outcome study.

Patients: 300 adult patients admitted to ICU with septic shock.

Intervention: Patients were randomly assigned to receive either HC (50 mg q6h) and FC (50 mg q24h) or placebo for 7 days.

Primary Outcome: 28-day survival in patients with relative adrenal insufficiency (nonresponders to corticotropin stimulation test).

Results: Of the 229 nonresponders, 53% of patients died in the steroid group versus 63% in the placebo group. This corresponds to a 15.9% relative risk reduction (P=0.02). There was no significant difference between groups in the responders.

Conclusion: Corticosteroid therapy in the ICU reduces mortality without increasing adverse events.

Corticosteroids for Treating Severe Sepsis and Septic Shock

Cochrane Database of Systematic Reviews 2004, Issue 1

Study: Meta-analysis of 15 randomized and quasi randomized control trials examining the efficacy of corticosteroids on death at one month in patients with severe sepsis and septic shock.

Results: Overall, there was no difference in 28-day all cause mortality. However, a subgroup of five trials that used long-term low dose corticosteroids (200-300 mg IV) showed a significant benefit in 28 day mortality (RR=0.80 95% CI 0.67-0.95). Data from this subgroup also showed a significant reduction of in-hospital mortality and increased shock reversal by day seven.

Conclusions: The lack of an overall benefit to corticosteroids in sepsis was attributed to significant study heterogeneity. Low dose and long-term corticosteroids appear to have significant benefit for patients with sepsis. However, further research is needed to identify patients with sepsis who have adrenal insufficiency. Moreover, the optimal time to start treatment and the optimal dose require further trials.

Early Goal-directed Therapy in the Treatment of Severe Sepsis and Septic Shock

NEJM 2001; 345(19):1368-77

Study: RCT of patients with severe sepsis or septic shock who arrived at an emergency department were randomized to receive early-goal directed therapy or standard therapy in the emergency department.

Intervention: Early-goal directed therapy consisted of specific treatment goals in the initial six hours of treatment. Specific goals were as follows:

CVP: 8-12 mmHg (Rx'd with either crystalloid or colloids)

MAP: >65 mmHg and <90 mmHg (Rx'd vasopressors or vasodilators)

ScvO₂: >70% (Rx'd with transfusion of pRBCs until hemotacrit >30, then inotropic agents).

Standard therapy in the emergency department consisted of ensuring MAP >65, CVP between 8-12 mmHg, and urine output >0.5 mg/kg/hr.

Results: The in-hospital mortality for patients assigned to early-goal directed therapy was 30.5% compared to 46.5% in the standard medical care group (p = 0.009). Patients in the early-goal directed therapy group had improved APACHE II scores, higher central venous oxygen saturation, lower lactate concentrations, higher pH, and a lower base deficit.

Conclusions: Early-goal directed therapy provides significant benefits to patients presenting to hospital with severe sepsis or septic shock. These patients had improved mortality and improved physiologic function as measured between 7 and 72 hours.

Early Goal Directed Therapy

- early goal-directed therapy that involves adjustments of cardiac preload, afterload and contractility to balance oxygen delivery with demand provides significant outcome benefits
- should be started immediately and completed within 6 hours of recognition of severe sepsis or septic shock
- patient should meet SIRS criteria and sBP <90 mmHg or lactate >4 mmol/L
 1. supplemental oxygen ± intubation and mechanical ventilation
 2. central venous and arterial catheterization
 3. if CVP <8 mmHg then crystalloid/colloid fluid IV to maintain CVP 8-12 mmHg
 4. MAP maintained 65-90 mmHg with the use of vasoactive agents
 5. if central venous oxygen saturation (ScvO₂) <70% then
 - ♦ transfusion of red cells until Hct >30%
 - ♦ if ScvO₂ <70% after transfusion then use inotropic agents
- supportive oxygenation and ventilation using lung-protective regimen
- early nutritional support: enteral route is used to preserve function of intestinal mucosal barrier
- control hyperglycemia with insulin to decrease infectious complications
- physiologic dose corticosteroid replacement therapy in patients with relative adrenal insufficiency (nonresponders to corticotropin stimulation test)
 - consider in mechanically ventilated septic shock patients with organ dysfunction requiring vasopressors, despite early goal-directed therapy and appropriate antibiotic therapy
- recombinant activated protein C may be considered in patients with severe sepsis or septic shock with an APACHE II score >25 despite early goal-directed therapy and appropriate antibiotic therapy
- DVT/PE prophylaxis
- advanced care planning, including the communication of likely outcomes and realistic goals of treatment with patients and families

Common Drug Overdoses

Table 32. Clinical Presentation and Management of Common Drug Overdoses

Drug Overdose	Clinical Syndrome	Specific Management
Acetaminophen	Nausea, vomiting, RUQ pain, abnormal liver enzymes and INR, jaundice, liver necrosis, coagulation defects	Gastric lavage Activated charcoal if <4 hrs post ingestion N-acetylcysteine
Amphetamines	HTN, tachycardia, tachypnea, arrhythmias, MI, vasospasm, seizures, diaphoresis, paranoid psychosis	Activated charcoal for oral ingestion Agitation/seizures: benzodiazepines HTN: α-antagonists, vasodilators (nitroglycerin, nifedipine)
Iron	Nausea, vomiting, GI discomfort, GI bleed, drowsiness, hypoglycemia, shock, coma, seizures, metabolic acidosis, coagulopathy, cardiac failure, hepatotoxicity, renal insufficiency, achloridia	Whole bowel irrigation, especially if abdominal x-ray evidence of pills Shock: Fluid resuscitation, vasopressors Iron chelating: deferoxamine IV
Tricyclic Antidepressants	CNS: sedation, confusion, seizures, delirium Cardiovascular: wide complex arrhythmias, hypotension	Prolonged QRS: alkalinizing blood (pH 7.5-7.55), IV sodium bicarbonate Seizures: benzodiazepines Hypotension: fluid resuscitation, vasopressors
Salicylate	Nausea, vomiting, tinnitus, vertigo, tachypnea, non-cardiac pulmonary edema, altered mental status, mixed respiratory alkalosis and metabolic acidosis	Activated charcoal if <4 hrs post ingestion Alkalize blood with sodium bicarbonate Consider hemodialysis if pulmonary edema, renal insufficiency, severely altered MS or plasma salicylate concentration >100 mg/dL

Common Medications

Table 33. Common Medications for Respiratory Diseases

	Drug	Adult Dose	Indications	Side Effects
BETA-2 AGONISTS				
Short-acting	salbutamol/albuterol (Ventolin®) (light blue/navy), terbutaline (Bricanyl®)	1-2 puffs q4-6h prn	Bronchodilator in acute reversible airway obstruction	CV (angina, flushing, palpitations, tachycardia, can precipitate Afib), CNS (dizziness, headache, insomnia, anxiety), GI (diarrhea, nausea, vomiting), rash, hypokalemia, paroxysmal bronchospasm
Long-acting	salmeterol (Serevent®), formoterol (Oxeze®)	1-2 puffs bid	Maintenance treatment (prevention of bronchospasm) in chronic obstructive lung disease, asthma	
Combination Long-acting beta-2 agonist and inhaled corticosteroid	fluticasone and salmeterol (Advair®) (purple discus) Budesonide and formoterol (Symbicort®) (red puffer)	1 puff bid	COPD and asthma	Common: CNS, headache, dizziness Resp: URTI, GI (N/V, diarrhea, pain/discomfort, oral candidiasis)
ANTICHOLINERGICS				
	ipratropium bromide (Atrovent®) (clear/green), tiotropium bromide (Spiriva®)	2-3 puffs qid 1 puff qam	Bronchodilator used in COPD, bronchitis and emphysema	Palpitations, anxiety, dizziness, fatigue, headache, nausea, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drugs
CORTICOSTEROIDS				
Inhaled	fluticasone (Flovent®) (orange/peach) budesonide (Pulmicort®) ciclesonide (Alvesco®)	2-4 puffs bid 2 puffs bid 1-4 puffs OD	Maintenance treatment of asthma	Headache, fever, N/V, MSK pain, URTI, throat irritation, growth velocity reduction in children/adolescents, HPA axis suppression, increased pneumonia risk in COPD
Systemic	beclomethasone (QVAR®, Vancril®) prednisone (Apo-prednisone®, Deltasone®) methylprednisolone (Depo-Medrol®, Solu-Medrol®)	1-2 puffs bid (40 µg), 1-2 puffs bid (80 µg) Typically 40-60 mg per day PO 125 mg q8h IV (sodium succinate) loading dose 2 mg/kg then 0.5-1 mg/kg q6h for 5 days	Acute exacerbation of COPD; severe, persistent asthma, PCP Status asthmaticus	Endocrine (hirsutism, DM/glucose intolerance, Cushing's syndrome, HPA axis suppression), GI (increased appetite, indigestion), ocular (cataracts, glaucoma), edema, AVN, osteoporosis, headache, psych (anxiety, insomnia), easy bruising
ADJUNCT AGENTS	theophylline (Elixophyllin®, Theo-Dur®)	5-13 mg/kg/day PO in divided doses, max 900 mg/day	Treatment of symptoms of reversible airway obstruction due to COPD	GI upset, diarrhea, N/V, anxiety, headache, insomnia, muscle cramp, tremor, tachycardia, PVCs, arrhythmias, Toxicity: persistent, repetitive vomiting, seizures
LEUKOTRIENE ANTAGONISTS				
	montelukast (Singular®)	10 mg PO qhs, now only available as once daily slow release	Prophylaxis and chronic treatment of asthma	Headache, dizziness, fatigue, fever, rash, dyspepsia, cough, flu-like symptoms
ANTIBIOTICS – COMMUNITY ACQUIRED PNEUMONIA				
Macrolide	erythromycin azithromycin clarithromycin	250-500 mg PO bid x 7-10 d 500 mg PO OD x 7-10 d 250-500 mg PO bid x 7-10 d	Alternate to doxycycline or fluoroquinolone	GI (abdominal pain, diarrhea, N/V), headache, prolonged QT, ventricular arrhythmias, hepatic impairment GI (diarrhea, N/V, abdo pain), renal failure, deafness Headache, rash, GI (diarrhea, N/V, abnormal taste, heartburn, abdo pain), increased BUN
Doxycycline		100 mg PO bid x 7-10 d	Alternate to macrolide or fluoroquinolone	Photosensitivity, rash, urticaria, anaphylaxis, diarrhea, enterocolitis, tooth discolouration in children
Fluoroquinolone	levofloxacin (Levaquin®) moxifloxacin (Avelox®)	500 mg PO OD x 7-10 d 400 mg PO OD x 7 d	Alternate to macrolide or doxycycline	CNS (dizziness, fever, H/A), GI (N/V, diarrhea, constipation), prolonged QT
ANTIBIOTICS – HOSPITAL ACQUIRED PNEUMONIA				
3rd gen Cephalosporin	ceftriaxone (Rocephin®)	1-2 g IV OD x 7-10 d	Combine with fluoroquinolone	Rash, diarrhea, eosinophilia, thrombocytosis, leukopenia, elevated transaminases
Fluoroquinolone	levofloxacin moxifloxacin	see above	Combine with 3rd gen cephalosporin	See above
Piperacillin/Taobactam (Tazocin®)		4.5 g IV q 6-8h x 7-10 d	Suspect Pseudomonas	CNS (confusion, convulsions, drowsiness), rash, Hematologic (abnormal platelet aggregation, prolonged PT, positive Coombs)
Vancomycin (Vancocin®)		1 g IV bid x 7-10 d	Suspect MRSA	CNS (chills, drug fever), hematologic (eosinophilia), rash, interstitial nephritis, renal failure, ototoxicity
Macrolide	azithromycin clarithromycin	500 mg IV OD x 2 d, then 500 mg PO OD x 5 d 250-500 mg PO bid x 7-10 d	Suspect Legionella	See above See above
ICU MEDICATIONS				
Pressors/Inotropes	norepinephrine (Levophed®) phenylephrine dobutamine	0.5-30 µg/min IV 0.5 µg/kg/min IV 2-20 µg/kg/min IV	Acute hypotension Severe hypotension Inotropic support	Angina, bradycardia, dyspnea, hyper/hypotension, arrhythmias See above See above
Sedatives/Analgesia	fentanyl (opioid class) propofol (anesthetic)	50-100 µg then 50-unlimited µg/hr IV 1-3 mg/kg then 0.3-5 mg/kg/hr IV	Sedation and/or analgesia Sedation and/or analgesia	Bradycardia, respiratory depression, drowsiness, hypotension Apnea, bradycardia, hypotension (good for ventilator sedation)

See Infectious Diseases, ID25 for the management of pulmonary tuberculosis

Landmark Respiriology Trials

Trial	Reference	Results
Pneumonia	<i>NEJM</i> 1978; 298:801-9	Interstitial lung disease subsets have different prognoses and response to treatment (e.g. desquamative but not usual interstitial pneumonia respond well to corticosteroids)
Lung Health	<i>JAMA</i> 1994; 272:1497-505	Aggressive smoking intervention significantly decreases the age-related decline in FEV ₁ in middle-aged smokers with mild airways obstruction
ARDS Network	<i>NEJM</i> 2000; 342:1301-8	Mortality decreased in ARDS patients ventilated with a low tidal volume strategy
Emphysema Treatment Trial	<i>NEJM</i> 2003; 348:2059-73	Lung volume reduction surgery benefits patients with upper lobe disease and low exercise capacity
CPAP and Apnea	<i>NEJM</i> 2005; 353:2025-33	CPAP ameliorates symptoms of sleep apnea but does not affect mortality in CHF
IELCAP	<i>NEJM</i> 2006; 355:1763-71	High survival rate in patients with early stage lung cancer detected by low dose CT screening
TORCH	<i>NEJM</i> 2007; 356:775-89	Combination of inhaled steroids and long-acting beta agonists improves COPD symptoms, reduces exacerbations and shows a trend to lowers mortality
UPLIFT	<i>NEJM</i> 2008; 359:1543-54	Tiotropium improves symptoms of COPD with fewer exacerbations, but does not affect FEV ₁ decline

References

- Andreoli, TE. Cecil Essentials of Medicine, sixth ed. WB Saunders Company. Philadelphia: 2004.
- Bach PB, Brown C, Gelfand SE. Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A summary and Appraisal of Published Evidence. *Annals of Internal Medicine* 2001;134:600-620.
- Augustino P, Ouellet K. Invasive approaches to treatment of venous thromboembolism. *Circulation* 2004;110(suppl 1): 1-27-1-34.
- Balk RA. Optimum treatment of severe sepsis and septic shock: evidence in support of the recommendations. *Disease-A-Month*. 2004;50(4):168-213.
- Bartlett JG, Dowell SF, Mandell LA et al. Practice Guidelines for the Management of Community-Acquired Pneumonia in Adults. *Clin Infect Dis* 2000;31:347-82.
- Bass JB Jr, Farer LS, Hopewell PC, O'Brien R, Jacobs RF, Ruben F, Snider DE Jr, Thornton G. Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and The Centers for Disease Control and Prevention. *Am J Respir Crit Care Med*. 1994 May; 149(5):1359-74.
- Baumann MH. Treatment of spontaneous pneumothorax. *Curr Opin Pulm Med*. 2000 Jul;6(4):275-80. Review.
- Boulet LP, Becker A, Berube D, Beveridge R, Ernst P. Canadian Asthma Consensus Report, 1999. *CMAJ* 1999;161 (11 Suppl):S1-61.
- Buller HR, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease. *Chest* 2004;126:401S-428S.
- Chunilal SD, Eikelboom JW, Attia J, et al. Dose this patient have pulmonary embolism? *JAMA* 2003;290:2849-2858.
- Crapo JD, Glassroth JL, Karlinsky JB, Talmadge EK. Baum's Textbook of Pulmonary Diseases, seventh ed. Lippincott Williams & Wilkins. USA: 2003.
- Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent J-L, Levy MM. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Critical Care Medicine* 2004; 32(3):536-55.
- Ferguson GT, Cherniack RM. Management of Chronic Obstructive Pulmonary Disease. *NEJM* 1993; 328:1017.
- Ferri, Fred F. Ferri's Clinical Advisor. Mosby/Elsevier Health Sciences: 2002.
- Ferri, Fred F. Practical Guide to the Care of the Medical Patient, fifth ed. Mosby/Elsevier Sciences. St.Louis: 2001.
- File TM. The epidemiology of respiratory tract infections. *Semin Respir Infect* 2000 Sep;15(3):184-94. Review.
- Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. *NEJM*. 1997 Jan 23;336(4):243-50.
- Gaine S. Pulmonary Hypertension. *JAMA* Dec 27, 2000. 284(25): 3160-3168.
- Garcia D, Ageno W, Libby E. Update on the diagnosis and management of pulmonary embolism. *Brit J Haematol* 2005;131:301-312.
- Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism. *Chest* 2004;126:338S-400S.
- Gorecka et Al. Effect of long term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax* 1997; 52(8):674-679.
- Gotfried M, Freeman C. An update on community-acquired pneumonia in adults. *Compr Ther* 2000 Winter;26(4):283-93. Review.
- Green DS, San Pedro GS. Empiric therapy of community-acquired pneumonia. *Semin Respir Infect*. 2000 Sep;15(3):227-33. Review.
- Health Canada: Population and Public Health Branch. Management of Severe Acute Respiratory Syndrome (SARS) in Adults: Interim Guidance for Health Care Providers. Ottawa: 2003 July 2. Available: http://www.hc-sc.gc.ca/pphb-dgspsp/sars-sras/pdf/sars-clin-guide-20030703_e.pdf (accessed 2003 Oct 26).
- Health Canada: Population and Public Health Branch. Recommended Laboratory Investigation of Severe Acute Respiratory. Ottawa: 2003 March 20. Available: http://www.hc-sc.gc.ca/pphb-dgspsp/sars-sras/sarslabrec_e.html (accessed 2003 Oct 26).
- Health Canada: Population and Public Health Branch. Early Detection of Severe or Emerging Respiratory Infections through Severe Respiratory Illness (SRI) surveillance. Ottawa: 2004 Feb 4. Available: <http://www.hc-sc.gc.ca/pphb-dgspsp/sars-sras/sri.html> (accessed 2004 August 5).
- Health Canada: Population and Public Health Branch. Outbreak Period. Ottawa: 2003 Nov 4. Available: http://www.hc-sc.gc.ca/pphb-dgspsp/sars-sras/sarscasedef_e.html (accessed 2004 August 5).
- Hershfield E. Tuberculosis: 9. Treatment. *CMAJ* 1999;161(4):405-11.
- Holleman D, Simel D. Does the clinical examination predict airflow limitation? *JAMA* 1995; 273:313-319.
- Hotchkiss RS and Karl IE. The pathophysiology and treatment of sepsis. *NEJM*. 2003;348(2):138-150.
- Lexi-Comp Inc. (Lexi-Drugs (Comp + SpecialtiesTM) Lexi-Comp Inc; Oct.12/2002 version
- Light RW, Macgregor MI, Luchsinger PC, et al. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med*. 1972;77(4): 507-13.
- Light RW. The management of parapneumonic effusions and empyema. *Curr Opin Pulm Med*. 1998 Jul;4(4):227-9. Review.
- Light RW. Useful tests on the pleural fluid in the management of patients with pleural effusions. *Curr Opin Pulm Med*. 1999 Jul;5(4):245-9. Review.
- Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, Isselbacher KJ. Eds. Harrison's Principles of Internal Medicine, sixteenth ed. McGraw-Hill Professional. USA: 2004.
- Long R, Njoo H, Hershfield E. Tuberculosis: 3. Epidemiology of the disease in Canada. *CMAJ* 1999;160(8):1185-90.
- Mantharamani NG, Koziel H. Chronic lung sepsis: lung abscess, bronchiectasis, and empyema. *Current Opinion in Pulmonary Medicine* 2003; 9:181-185.
- McCloud TC, Swenson SJ. Lung carcinoma. *Clin Chest Med*. 1999 Dec;20(4):697-713, vii. Review.
- McPhee SJ, Papadakis MA, Tierney LM. Current Medical Diagnosis and Treatment 2007, forty-seventh ed. McGraw-Hill Professional. USA: 2006.
- Nguyen HB, Rivers EP, Abrahamian FM, Moran GJ, Abraham E, Trzeciak S, Huang DT, Osborn T, Stevens D. Severe sepsis and septic shock: Review of the literature and emergency department management guidelines. *Ann Emerg Med*. 2006. July; 48(1): 28-54.
- O'Donnell DE, Aaron S, Bourbeau J et al. Canadian thoracic society recommendations for management of chronic obstructive pulmonary disease. *Can Respir J*. 2003; May-June;11(1) Suppl A: 17A.

- Ost D, Fein A. Evaluation and management of the solitary pulmonary nodule. *Am J Respir Crit Care Med*. 2000 Sep;162(3 Pt 1):782-7. Review.
- Ost D, Fein AM and Feinsilver SH. The solitary pulmonary nodule. *NEJM*. 2003 348: 2535-2542.
- Parfrey H, Chilvers ER. Pleural disease—diagnosis and management. *Practitioner*. 1999 May;243(1598):412, 415-21. Review.
- Pauwels RA, Buist AS, Calverly PM. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary. *American Journal of Respiratory and Critical Care Medicine*. 2001;163:1256-1276.
- Peiris JSM, Kwok DP, Osterhaus, ADME, Stohr K. The Severe Acute Respiratory Syndrome. *NEJM*. 2003 Dec;349(25):2431-41.
- Ram FSF, Picot J, Lightowler J, Wedzicha, JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2004; 3:CD004104.
- Reimer LG. Community-acquired bacterial pneumonias. *Semin Respir Infect*. 2000 Jun;15(2):95-100. Review.
- Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *NEJM*. 2001; 345(19): 1368-1377.
- Sabatine MS. 2004. Pocket Medicine: The Massachusetts General Hospital Handbook of Internal Medicine. Philadelphia: Lippincott Williams and Wilkins. pp. 6-1 & 5-2.
- Scharschmidt, Bruce F. Pocket Medicine: Internal Medicine Pulmonary Medicine. *PocketMedicine.com*: 2002.
- Stein PD, Saltzman, HA, Weg, JG. Clinical characteristics of patients with acute pulmonary embolism. *Am J Cardiol* 1991; 68:1723.
- Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. *NEJM* 2006;354:2317-2327.
- Tarascon Inc. 2004. Tarascon Pocket Pharmacopoeia™ 2004 edition. Lompoc: Tarascon Publishing.
- Thrombosis Interest Group of Canada. Clinical Guides. 27 brief, evidence-based guides on thrombosis for general practitioners, downloadable to a pda. Available: www.tigc.org.
- US Centers for Disease Control and Prevention (CDC). Severe acute respiratory syndrome (SARS): Information for Clinicians. Atlanta: The CDC; 2003 Oct 14. Available: <http://www.cdc.gov/ncidod/sars/clinicians.htm> (accessed 2003 Oct 26).

Notes_____

Pamela Tsao, Bertha Wong and Lianne Wong, chapter editors

Doreen Ezeife and Nigel Tan, associate editors

Steven Wong, EBM editor

Dr. Dana Jerome and Dr. Heather McDonald-Blumer, staff editors

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Basic Anatomy Review

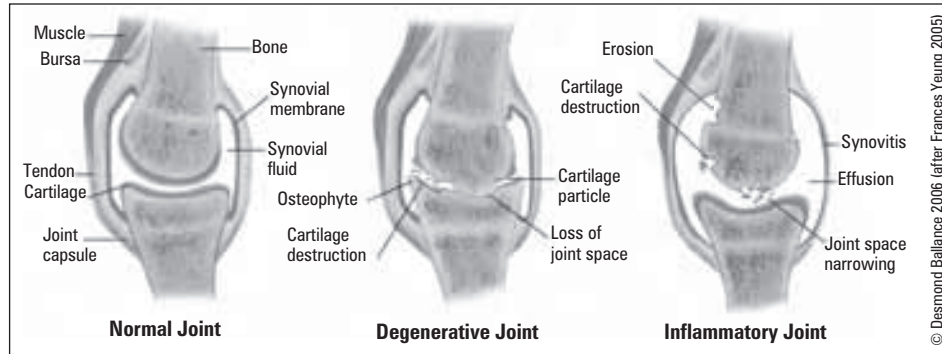


Figure 1. Structure of Normal, Degenerative and Inflammatory Joint

Basics of Immunology

Immune Mechanisms of Disease



Terminology in Rheumatology

Arthritis: joint swelling/effusion, OR 2 of the following:

- Decreased range of motion
- Tenderness or pain on motion
- Increased warmth

Arthralgia: perception of joint pain without obvious clinical findings

Active joint: swelling, joint tenderness or stress tenderness

- fundamental principles of pathogenesis of autoimmune diseases
 - disease results from a failure to discriminate between self and non-self
 - activated immune system against self → cell damage/destruction/dysfunction
 - autoreactive T-cells are common effectors in these diseases
- mechanisms of immunologically mediated disorders (4 types of immune reactions):
 - **anaphylactic (type I)**
 - ♦ formation of IgE → release of immunologic mediators from basophils/mast cells → diffuse inflammation
 - ♦ e.g. asthma, allergic rhinitis, anaphylaxis
 - **cytotoxic (type II)**
 - ♦ formation of antibody (Ab) → deposit and bind to antigen (Ag) on cell surface → phagocytosis or lysis of target cell
 - ♦ e.g. autoimmune hemolytic anemia, Goodpasture's syndrome, Graves' disease, pernicious anemia
 - **immune complex (type III)**
 - ♦ formation of Ag-Ab complexes → activate complement → attract inflammatory cells and release of cytokines
 - ♦ e.g. SLE, PAN, post-streptococcal glomerulonephritis, serum sickness
 - **cell-mediated/delayed hypersensitivity (type IV)**
 - ♦ release of cytokines by sensitized T-cells and T-cell mediated cytotoxicity
 - ♦ e.g. contact dermatitis

Immunogenetics and Disease

- cell surface molecules called human leukocyte antigen (HLA) play a role in mediating immune reactions
- major histocompatibility complex (MHC) are genes on the short arm of chromosome 6 that encode HLA molecules
- there are three classes of MHC (see Table 1)
- discrete domains of hypervariability within MHC molecules thought to represent "susceptibility determinants"
- certain HLA haplotypes are associated with increased susceptibility to autoimmune diseases (see Table 2)

Table 1. Classes of Major Histocompatibility Complexes (MHCs)

MHC Class	Types	Location	Function
I	HLA-A, -B, -C	All cells	Recognized by CD8+ (cytotoxic) T-lymphocytes
II	HLA-DP, -DQ, -DR	Antigen presenting cells (mononuclear phagocytes, B cells, others)	Recognized by CD4+ (helper) T-lymphocytes
III	Complement components	In plasma	Chemotaxis, opsonization, lysis of bacteria and cells

Table 2. HLA-Associated Rheumatic Disease

HLA Type	Associated Conditions	Comments
B27	Ankylosing spondylitis (AS) Reactive arthritis (ReA) Enteropathic arthritis (spine)	In AS, relative risk = 70-90 times In ReA, relative risk = 40 times
DR4, DR1	Rheumatoid arthritis (RA)	In RA, relative risk = 2-10 times; found in 93% of patients
DR3	Sjögren's syndrome SLE	DR3 associated with many non-rheumatic conditions (celiac disease, Type 1 DM, Graves' disease, chronic active hepatitis)

Differential Diagnoses of Common Presentations

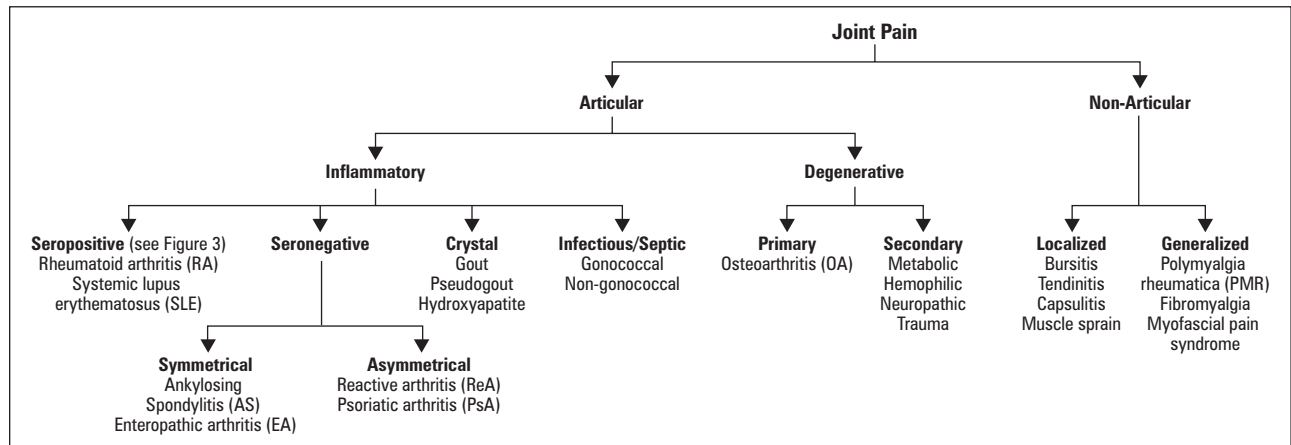


Figure 2. Clinical Approach to Joint Pain

Table 3. Inflammatory vs. Degenerative Symptoms

Inflammatory	Degenerative
Pain at rest, relieved by motion	Pain with motion, relieved by rest
Morning stiffness >1 hr	Morning stiffness <1/2 hr
Warmth, erythema, swelling	Joint instability, buckling, locking
Malalignment/deformity	Bony enlargement, malalignment/deformity
Extra-articular manifestations	

Table 4. Seropositive vs. Seronegative Rheumatic Diseases

	Seropositive	Seronegative
Demographics	F>M	M>F
Peripheral Arthritis	Symmetrical Small and large joints DIP less involved	Usually asymmetrical Usually larger joints, lower extremities (psoriatic arthritis may be the exception) DIP in psoriatic arthritis Dactylitis ("sausage digit") Enthesitis
Pelvic/Axial Disease	No (except for C-spine)	Yes
Enthesitis	No	Yes
Extra-Articular	Nodules Vasculitis Sicca Raynaud's phenomenon	Iritis (= anterior uveitis) Oral ulcers GI GU



Causes of Joint Pain

SOFTER TISSUE

Sepsis
OA
Fracture
Tendon/muscle
Epiphyseal
Referred
Tumour
Ischemia
Seropositive arthritides
Seronegative arthritides
Urate (gout)/other crystal
Extra-articular rheumatism (PMR/fibromyalgia)



Patterns of Joint Involvement

Symmetrical vs. asymmetrical
Small vs. large
Mono vs. oligo vs. polyarticular
Axial vs. peripheral

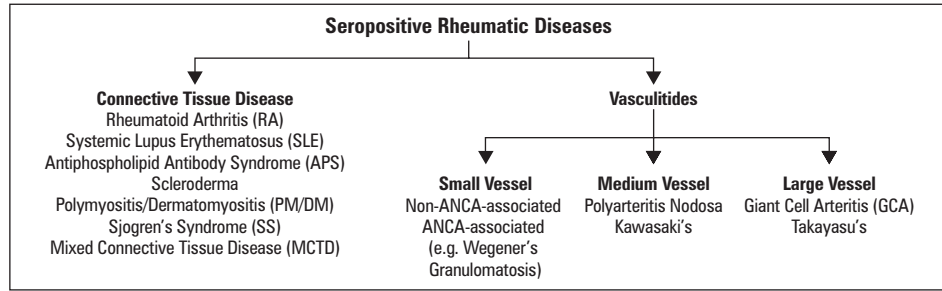


Figure 3. Seropositive Rheumatic Diseases

Septic Arthritis

- for any monoarticular arthritis one must rule out septic etiology; consider empiric antibiotic treatment until septic arthritis is excluded by history, physical exam and synovial fluid analysis (see [Infectious Diseases, ID24/Orthopaedics, OR8](#))

Degenerative Arthritis: Osteoarthritis (OA)

Definition

- primary (idiopathic)
 - most common, of unknown etiology
- secondary
 - post-traumatic or mechanical
 - post-inflammatory (e.g. RA) or post-infectious
 - heritable skeletal disorders (e.g. scoliosis)
 - endocrine disorders (e.g. acromegaly, hyperparathyroidism, hypothyroidism)
 - metabolic disorders (e.g. gout, pseudogout, hemochromatosis, Wilson's disease, ochronosis)
 - neuropathic (also known as Charcot joints)
 - atypical joint trauma due to loss of proprioceptive senses (e.g. diabetes, syphilis)
 - avascular necrosis (e.g. fracture, steroids, alcohol, gout, sickle cell)
 - other (e.g. congenital malformation)

Etiology and Pathophysiology

- altered joint function and damage
- primary event is deterioration of articular cartilage due to local biomechanical factors and release of proteolytic and collagenolytic enzymes
 - OA develops when cartilage catabolism > synthesis
 - loss of proteoglycans and water exposes underlying bone
- abnormal local bone metabolism further damages joint
- synovitis is secondary to cartilage damage therefore may see small effusions in OA

Epidemiology

- most common arthropathy (12% of age 25-74)
- increased prevalence with increasing age (35% of 30-year olds, 85% of 80-year olds)

Risk Factors

- genetic predisposition, advanced age, obesity (for knee OA), female, trauma

Signs and Symptoms

- localized to affected joints (not a systemic disease)
- pain is often insidious, gradually progressive, with intermittent flare-ups and remissions

Table 5. Signs and Symptoms of OA

Signs	Symptoms
Joint line tenderness; stress pain	Joint pain with motion; relieved with rest
Bony enlargement at affected joints	Short duration of stiffness (< 1/2 hr) after immobility
Malalignment/deformity (angulation)	Joint instability/buckling
Limited ROM	Joint locking due to "joint mouse" (bone or cartilage fragment)
Crepitus on passive ROM	Loss of function or other internal derangements (e.g. meniscal tear)
Inflammation (mild if present)	
Periarticular muscle atrophy	

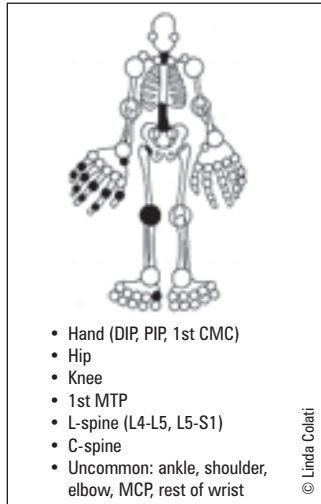
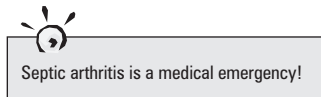


Figure 4. Common Sites of Involvement in OA

Intraarticular Corticosteroid for Treatment of Osteoarthritis of the Knee
Cochrane Database of Syst Rev 2006; 2:CD005328.
Study: Cochrane systematic review. 28 RCT and quasi-RCT trials.
Population: Patients with osteoarthritis (OA) of the knee.
Intervention: Intraarticular (IA) corticosteroid injection.
Results: IA corticosteroids were more effective than placebo for pain reduction and global assessment at one week post-injection. There was significant pain reduction at 2 and 3 weeks, but no benefit for pain and function beyond 4 weeks post-injection. There was no benefit for global function beyond 1 week post-injection. There were higher rates of pain reduction at 4 weeks post-injection for triamcinolone hexacetonide versus betamethasone. There was no difference between IA corticosteroids and joint lavage in outcomes or safety. Hyaluronic acid (HA) injections showed better response than IA corticosteroids between 5 and 13 weeks post-injection.
Conclusion: IA corticosteroid injection is effective for the short-term treatment of OA of the knee with few side effects. HA therapy can provide more durable results.

Joint Involvement (see Figure 4)

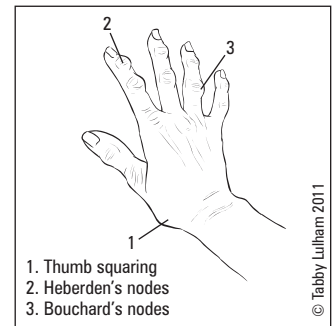
- asymmetric
- hand (see Figure 5)
 - DIP (Heberden's nodes = osteophytes → enlargement of joints)
 - PIP (Bouchard's nodes)
 - CMC (usually thumb squaring)
 - MCP is usually spared (except the 1st MCP)
- hip
 - usually presents as groin pain but other sites are also found
 - dull or sharp pain in trochanter, anterior thigh, or knee
 - internal rotation and abduction are lost first
- knee
 - initial narrowing of one compartment, medial > lateral
 - standing x-rays must be done (not supine)
- foot
 - common in first MTP
- lumbar spine
 - very common especially L4-L5, L5-S1
 - degeneration of intervertebral discs and facet joints
 - reactive bone growth can contribute to neurological impingement (e.g. sciatica, neurogenic claudication) or spondylolisthesis (displacement of vertebrae)
- cervical spine
 - commonly presents with neck pain, especially in lower cervical area

Investigations

- blood work
 - normal CBC and ESR
 - negative RF and ANA
- radiology: 4 hallmark findings (see sidebar)
- synovial fluid: non-inflammatory (see Table 25)

Treatment

- presently no treatment alters the natural history of OA
- non-pharmacological therapy
 - weight loss (minimum 5-10 lb loss) if overweight
 - rest/low-impact exercise
 - physiotherapy: heat/cold, exercise programs
 - occupational therapy: aids, splints, cane, walker, bracing
- pharmacological therapy (see Table 28)
 - oral: acetaminophen, NSAIDs
 - joint injections: hyaluronic acid, corticosteroid
 - topical: capsaicin, NSAIDs
 - glucosamine ± chondroitin
- surgical treatment
 - joint replacement

**Figure 5. Hand Findings in OA**

OA of MCP joints can be seen in hemochromatosis or chondrocalcinosis.



Hint: Bouchard's is closer to the Body

**The Radiographic Hallmarks of OA**

1. Joint space narrowing
2. Subchondral sclerosis
3. Subchondral cysts
4. Osteophytes

Glucosamine Therapy for Treating Osteoarthritis
Cochrane Database of Systemic Reviews 2005; 2:CD002946. DOI: 10.1002/14651858. CD002946. pub2

Study: Meta-analysis of 20 RCTs (n=2750) examining the efficacy of glucosamine on OA.
Results: Overall analysis of 15 RCTs favoured glucosamine over placebo for total reduction in pain (measured by a variety of methods). Significant differences between glucosamine and placebo were also observed when compared to Lequesne Index scores. Only the glucosamine containing Rotta preparation was found to be significant. No significant differences in WOMAC (pain, stiffness and function subscales) were found between glucosamine and placebo when only studies with adequate allocation concealment were included. There was evidence to suggest that glucosamine may slow the radiologic progression of OA at 3 years. Glucosamine had an excellent safety profile.
Conclusion: Glucosamine appears helpful for pain when all studies (low quality and older studies) are included. However, when only the higher quality studies are included, there is no longer a difference between glucosamine and placebo. Glucosamine was very well tolerated with low toxicity. Rotta preparation of glucosamine may be of some benefit.

Meta-analysis: Chondroitin for Osteoarthritis of the Knee and Hip
Annals of Internal Medicine 2007; 146(8):580-590

Study: Meta-analysis of 20 RCTs (n=3846) examining the efficacy of chondroitin on OA.
Results: The analysis of this review was hampered by significant trial heterogeneity. Trials with poor methodology (small numbers, inadequate randomization concealment, no intention to treat analysis) showed larger effect sizes in favour of glucosamine than more recent trials. When the authors analyzed only the newer and more robust trials, an effect size of -0.3 (CI 95%: -0.13 to 0.07) was generated.
Conclusion: There is high quality evidence to suggest there is no difference between chondroitin and placebo. Chondroitin should be disregarded from routine use in clinical practice.

Seropositive Rheumatic Disease: Connective Tissue Disorders

Table 6. Features of Seropositive Arthropathies

	RA	SLE	Scleroderma	Dermatomyositis
Clinical Features				
History	Symmetrical Polyarthritides (small joint involvement) AM stiffness (>1 hr)	Multisystemic disease: rash, photosensitivity, Raynaud's, alopecia, cardiac and pulmonary serositis, CNS symptoms, glomerulonephritis	Skin tightness, stiffness of fingers, Raynaud's, heartburn/dysphagia, pulmonary hypertension, renal dysfunction	Heliotrope rash (eyelids), Gottron's papules, macular erythema and poikiloderma (shoulders, neck and chest), proximal muscle weakness ± pain
Physical Examination	Effused joints Tenosynovitis Nodules Joint deformities Bone-on-bone crepitus	Confirm historical findings (rash, serositis, etc.) ± effused (typically small) joints (can be minimal, look for soft tissue swelling)	Skin tightness on dorsum of hand, facial skin tightening, telangiectasia, calcinosis, non-effused joint	Rash, proximal muscle weakness

Table 6. Features of Seropositive Arthropathies (continued)

	RA	SLE	Scleroderma	Dermatomyositis
Laboratory				
Non-specific	Increased ESR in 50-60% Increased platelets Decreased Hb Decreased WBC (Felty's)	Increased ESR Decreased platelets (autoimmune) Decreased Hb (autoimmune) Decreased WBC (leukopenia, lymphopenia)	Increased ESR Increased platelets Decreased Hb Normal WBC	Possible increased ESR Normal platelets Decreased Hb Normal WBC
Specific	RF +ve in ~80%	ANA +ve in 98% Anti-dsDNA +ve in 50-70% Anti-SM +ve in 30% Decreased C3, C4, total hemolytic complement False positive VDRL (in lupus subtypes) Increased PTT (in lupus subtypes; e.g. antiphospholipid Ab)	ANA +ve in >90% Anti-topoisomerase 1 (diffuse) Anti-centromere (usually in CREST, see RH11)	CK elevated in 80% ANA +ve in 33% anti-Jo-1, anti-Mi-2 Muscle biopsy EMG MRI
Synovial Fluid	Inflammation Leukocytosis (>10,000)	Mild inflammation with +ve ANA	Not specific	Not specific
Radiographs	Periarticular osteopenia Joint space narrowing Erosions Absence of bone repair Symmetric/concentric	Nonerosive ± osteopenia ± soft tissue swelling	± pulmonary fibrosis ± esophageal dysmotility ± calcinosis	± esophageal dysmotility ± interstitial lung disease ± calcifications

**Common Presentation**

- Morning stiffness > 1 hr, improves with use
- Symmetric joint involvement
- Initially involves small joints of hands and feet
- Constitutional symptoms

**1987 American Rheumatism Association RA criteria**

At least 4 of:

- Morning stiffness > 1 hour for > 6 weeks
- Arthritis ≥ 3 joints for > 6 weeks
- Arthritis of hand joints for > 6 weeks
- Symmetric arthritis for > 6 weeks
- Rheumatoid nodules
- Serum RF positive
- Radiographic changes (erosions or periarticular osteopenia)

Criteria are 91-94% sensitive and 89% specific for RA.



- PIP
- MCP
- Wrist, not 1st CMC
- Elbow
- Shoulder
- Knee
- Ankle
- MTP
- C-spine

© Linda Colati

Rheumatoid Arthritis (RA)

**Definition**

- chronic, symmetric, erosive synovitis of peripheral joints (i.e. wrists, MCPs, MTPs)
- characterized by a number of extra-articular features

Table 7. Classification Criteria for RA: total score of 6 or more classifies patient as definite RA. Patient must have at least 1 joint with definite clinical swelling, not better explained by another disease

Criteria	Score
1. Joint involvement (swollen or tender)	
1 large joint (shoulders, elbows, hips, knees, and ankles)	0
2-10 large joints	1
1-3 small joints (MCPs, PIPs, wrists, 2nd-5th MTPs)	2
4-10 small joints	3
> 10 joints (at least 1 small joint)	5
2. Serology	
Negative RF and negative Anti-CCP	0
Low-positive RF or low-positive Anti-CCP (<3x ULN)	2
High-positive RF or high-positive Anti-CCP (>3x ULN)	3
3. Acute phase reactants	
Normal CRP and normal ESR	0
Abnormal CRP and abnormal ESR	1
4. Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

See sidebar for 1987 RA criteria.

Reference: *Arthritis and Rheumatism* 2010; 62(9):2569-2581**Etiology and Pathophysiology**

- autoimmune disorder, unknown etiology
- hallmark of RA is hypertrophy of the synovial membrane
 - activated rheumatoid synovium (pannus) grows into and over the articular surface resulting in destruction of articular cartilage and subchondral bone
- two theories attempt to explain chronic remissions and exacerbations seen in RA
 - **sequestered Ag**
 - ♦ during inflammation, immune complexes (ICs) are deposited at avascular cartilage-bone junction → ICs (free of reticulo-endothelial system) get released as further cartilage breaks down → triggers inflammatory cascade
 - **molecular mimicry**
 - ♦ cartilage damage → altered cartilage resembles undefined offending agent → triggers inflammatory cascade

Figure 6. Common Sites of Joint Involvement in RA

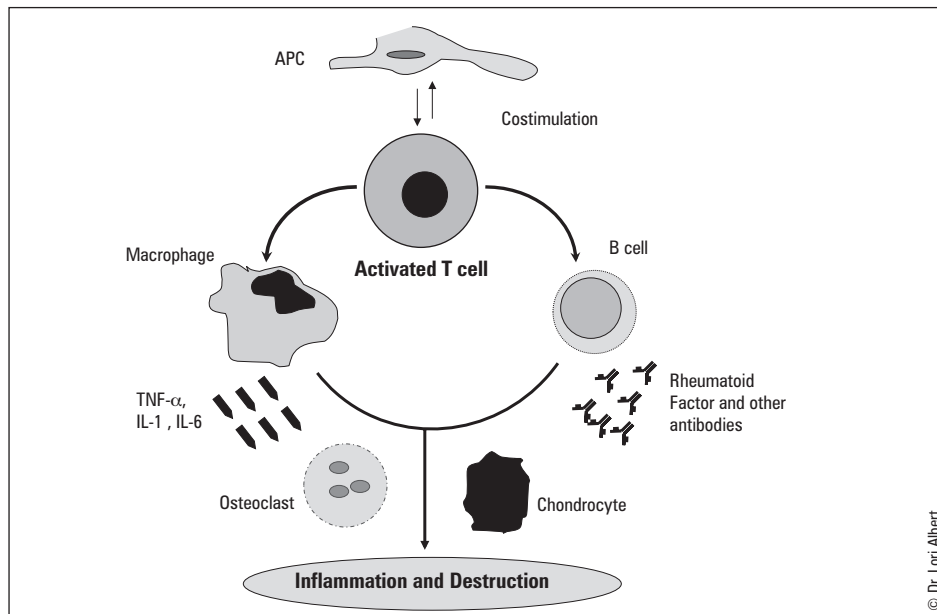


Figure 7. Immune Pathways in RA

Epidemiology

- incidence 0.6-2.9 per 1,000 population/yr, prevalence 1% of adult population
- F:M = 3:1; age of onset 20-40 yrs
- genetic predisposition: HLA-DR4/DR1 association (93% of patients have either HLA type)

Signs and Symptoms

- variable course of exacerbations and remissions
- morning stiffness >1 hr, improves with use, aggravated by rest
- symmetric joint involvement (see Figure 6)
- joint swelling, tender joints
- signs of mechanical joint damage: loss of motion, instability, deformity, crepitus
- constitutional symptoms: profound fatigue; rarely myalgia or weight loss
- extra-articular features (EAF) (see Table 8)
- limitation of function and decrease in global functional status
- complications of chronic synovitis
 - joint deformities (see Figure 8)
 - swan neck deformity, boutonnière deformity
 - ulnar deviation of MCP; radial deviation of wrist joint
 - hammer toe, mallet toe, claw toe
 - flexion contractures
 - atlanto-axial and subaxial subluxation
 - C-spine instability
 - neurological impingement (long tract signs)
 - difficult intubation
 - limited shoulder mobility, spontaneous tears of the rotator cuff leading to chronic spasm
 - tenosynovitis → may cause rupture of tendons
 - carpal tunnel syndrome
 - ruptured Baker's cyst (outpouching of synovium behind the knee); presentation similar to acute DVT

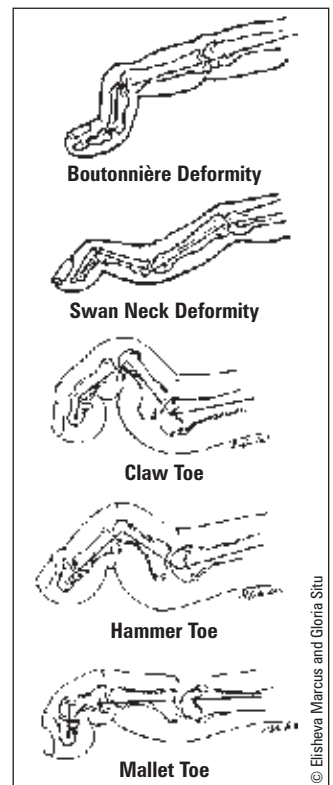


Figure 8. Joint Deformities



Syndromes in RA

- Sjögren's syndrome (common): keratoconjunctivitis sicca and xerostomia (dry eyes and mouth)
- Caplan's syndrome (rare): multiple pulmonary nodules and pneumoconiosis
- Felty's syndrome (rare): arthritis, splenomegaly, neutropenia



Poor prognostic features of RA include young age of onset, high RF titer, elevated ESR, activity of >20 joints, and presence of EAF.

Table 8. Extra-Articular Features of RA Classified by Underlying Pathophysiology

System	Vasculitic	Lymphocytic Infiltrate
Skin	Periungual infarction, cutaneous ulcers, palpable purpura	Rheumatoid nodules
Ocular	Episcleritis, scleritis	Keratoconjunctivitis sicca (see sidebar)
Head and Neck		Xerostomia (see sidebar), Hashimoto's thyroiditis (see Endocrinology, E27)
Cardiac		Peri-/myocarditis, valvular disease, conduction defects
Pulmonary		Pulmonary fibrosis, pleural effusion, pleuritis, pulmonary nodules
Neurologic	Peripheral neuropathy: sensory stocking-glove, mononeuritis multiplex	
Hematologic		Splenomegaly, neutropenia (Felty's, see sidebar)

**Side Effects of Steroids**

- Weight gain
- Osteoporosis, avascular necrosis (AVN)
- Cataracts, glaucoma
- Peptic ulcer disease (PUD)
- Susceptibility to infection
- Easy bruising
- Acne
- Hypertension
- Hyperlipidemia
- Hypokalemia, hyperglycemia
- Mood swings



Only DMARDs (not analgesics or NSAIDs) alter the course of RA!

Comparison of Treatment Strategies in Early Rheumatoid Arthritis

Ann Intern Med 2007; 146(6)

Study: RCT of 508 patients comparing 4 different treatment strategies for early rheumatoid arthritis (known as the BEST trial).

Intervention:

Group 1: Sequential Monotherapy with traditional DMARDs

Group 2: Step-Up Combination Therapy

Group 3: Initial Combination Therapy with prednisone (high dose)

Group 4: Initial Combination Therapy with infliximab

Results: Patients in groups 3 and 4 responded faster and had significantly greater overall change in physical function scores after the first year of treatment. By end of the second year, groups 1 and 2 had achieved a similar response to groups 3 and 4. Groups 3 and 4 also showed significantly less radiologic progression of their disease over 2 years than groups 1 and 2. There were no significant differences in toxicity levels between the 4 groups.

Conclusions: Initial combination therapy with prednisone or infliximab results in faster response rates. Whether faster initial response rates leads to better long-term disease outcomes has not yet been studied.

The Safety of Infliximab, Combined with Background Treatments, among Patients with Rheumatoid Arthritis and Various Comorbidities (START)

Arthritis Rheum 2006; 54:1075-86

Study: Randomized, placebo-controlled multicentre trial.

Patients: 1084 patients (mean age 52 yrs, 80% female) with active moderate to severe rheumatoid arthritis despite treatment with methotrexate.

Intervention: Patients were randomized to receive infusions of placebo, infliximab dosed at 3 mg/kg, or infliximab dosed at 10 mg/kg at 0, 2, 6, and 14 weeks, in addition to methotrexate therapy.

Primary Outcome: Incidence of serious infection within 22 weeks of randomization.

Results: Compared with the placebo group, the relative risk of developing serious infection was 1.0 (95%CI 0.3-3.1, $P=0.995$) in patients receiving infliximab at 3 mg/kg and 3.1 (95%CI 1.2-7.9, $P=0.013$) in patients receiving infliximab at 10 mg/kg. In addition, 31% of patients receiving infliximab at 3 mg/kg and 32% of patients receiving infliximab at 10 mg/kg were able to achieve remission at 22 weeks compared with only 14% of those receiving placebo ($P<0.001$, NNT=6).

Conclusions: Therapy with infliximab 3 mg/kg does not significantly increase the risk of serious infection in patients with active moderate to severe rheumatoid arthritis already receiving methotrexate. However, therapy with infliximab 10 mg/kg does significantly increase the risk of serious infection in this population.

Classification of Global Functional Status in RA (American College of Rheumatology, 1991)

- **Class I:** able to perform usual ADLs (self-care, vocational, avocational)
- **Class II:** able to perform self-care and vocational activities, restriction of avocational activities
- **Class III:** able to perform self-care, restriction of vocational and avocational activities
- **Class IV:** limited ability to perform self-care, vocational, avocational activities

Investigations

- bloodwork
 - RF sensitivity ~80% but non-specific (see Table 19); may not be present at onset of symptoms
 - anti-CCP (cyclic citrullinated peptide): sensitivity ~80%; may precede onset of symptoms
 - increased disease activity is associated with decreased Hb (anemia of chronic disease), increased platelets, elevated ESR, CRP, and RF
- imaging
 - x-rays are essential for following this disease (see Table 6)
 - ultrasound, MRI may be used in imaging hands to detect early synovitis and erosions

Treatment

- goals of therapy
 - control disease activity
 - relieve pain and stiffness
 - maintain function and lifestyle
 - prevent or control joint damage
 - key is early diagnosis and early intervention with disease modifying anti-rheumatic drugs (DMARDs)

Education, Occupational Therapy, Physiotherapy, Vocational Counselling

- The Arthritis Society (Canada) and Arthritis Foundation (U.S.) for educational resources
- therapeutic exercise program (isometrics and active, gentle ROM exercise during flares, aquatic/aerobic/strengthening exercise between flares), assistive devices as needed
- patients may need job modification, time off work or change in occupation

Medical**1. Reduction of Inflammation and Pain**

- NSAIDs
 - individualize according to efficacy and tolerability
 - contraindicated or cautioned in some patients (e.g. PUD, pregnancy, see Table 28)
- analgesics
 - add acetaminophen ± opioid prn for synergistic pain control
- corticosteroids
 - local
 - ♦ intra-articular injections to control symptoms in a specific joint
 - ♦ eye drops for eye involvement
 - systemic (prednisone)
 - ♦ low dose (5-10 mg/day) useful for (a) short term to improve symptoms if NSAIDs ineffective, (b) to bridge gap until DMARD takes effect or (c) for refractory disease
 - ♦ moderate to high dose (20-60 mg/day) for cardiopulmonary disease
 - ♦ high dose (1 mg/kg/day) for vasculitis
 - ♦ do baseline DEXA bone density scan and start bisphosphonate, calcium, and vitamin D therapy if using corticosteroids >3 months at >7.5 mg/day
 - ♦ cautions/contraindications: active infection, osteoporosis, hypertension, gastric ulcer, diabetes, TB

2. Disease Modifying Anti-Rheumatic Drugs (DMARDs) (see Table 29)

- DMARDs are the standard of care
- start DMARDs when diagnosis is confirmed to decrease disease progression, symptoms and signs
- DMARDs reduce or prevent joint damage, and are associated with better long-term disability index
- delayed onset of action (may take 8-12 weeks)
- many DMARDs have potential toxicities that require periodic monitoring
- if repetitive flares, progressive joint damage, or ongoing disease activity after 3 months of maximal therapy → change or add other DMARDs
- **non-biologics**
 - choice depends on: disease duration, disease activity, presence of poor prognostic features
 - methotrexate is the gold standard
 - others: hydroxychloroquine, sulfasalazine, leflunomide
 - combination therapy with methotrexate is now standard of care
- **biologics: indicated if persistent disease activity**
 - commonly used after failure of other DMARDs; however, evidence suggests benefit of use in early RA as well (e.g. infliximab, etanercept, etc.)

Surgical Therapy

- surgery indicated for structural joint damage
- synovectomy: debridement and/or removal of inflamed synovium from individual joints (surgical or radioactive)
- joint replacement (hip, shoulder, knee, less commonly MCP, ankle, elbow)
- joint fusion (wrist, thumb, ankle, C-spine)
- reconstruction (tendon repair)

Systemic Lupus Erythematosus (SLE)

Definition

- chronic inflammatory multisystem disease of unknown etiology, characterized by production of autoantibodies and diverse clinical manifestations

Table 9. Diagnostic Criteria of SLE: 4 or more of 11 must be present serially or simultaneously

Criteria	Description
Clinical	
Malar rash	Classic "butterfly rash", sparing of nasolabial folds, no scarring
Discoid rash	May cause scarring due to invasion of basement membrane
Photosensitivity	Skin rash in reaction to sunlight
Oral/nasal ulcers	Usually painless
Arthritis	Symmetric, involving ≥ 2 small or large peripheral joints, non-erosive
Serositis	Pleuritis or pericarditis
Neurologic disorder	Seizures or psychosis
Laboratory	
Renal disorder	Proteinuria (>0.5 g/day or 3+) <ul style="list-style-type: none"> Cellular casts (RBC, Hb, granular, tubular, mixed)
Hematologic disorder	Hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia
Immunologic disorder	Anti-dsDNA, anti-Sm <ul style="list-style-type: none"> Antiphospholipid antibodies based on the finding of serum anticardiolipin Ab, lupus anticoagulant, or false positive VDRL
Antinuclear antibody (ANA)	Most sensitive test (98%), not specific

Note: "4, 7, 11" rule \rightarrow 4 out of 11 criteria (4 lab, 7 clinical) for diagnosis
American College of Rheumatology, 1997 update

Etiology and Pathophysiology

- production of autoantibodies causing multi-organ inflammation
- multifactorial etiology (see Figure 9)
- **genetics**
 - common association with HLA-B8/-DR3; ~10% have positive family history
- **estrogen**
 - prepubertal and postmenopausal women have similar incidence to men
 - men with SLE have higher concentration of estrogenic metabolites
- **infection**
 - viral (nonspecific stimulant of immune response)
- **drugs**
 - anticonvulsants (phenytoin)
 - antihypertensives (hydralazine)
 - antiarrhythmics (procainamide)
 - isoniazid (INH)
 - anti-histone antibodies are commonly seen in drug-induced lupus
 - oral contraceptive pills associated with exacerbation
 - biologic response modifiers

Epidemiology

- prevalence: 0.05% overall
- F:M = 10:1; age of onset in reproductive years, 13-40
- more common and severe in African-Americans and Asians
- bimodal mortality pattern
 - early (within 2 years)
 - ♦ active SLE, active nephritis, infection secondary to steroid use
 - late (>10 years)
 - ♦ inactive SLE, inactive nephritis, atherosclerosis likely due to chronic inflammation



Diagnostic Criteria of SLE

MD SOAP BRAIN

Malar rash	Blood
Discoid rash	Renal
Serositis	Arthritis
Oral ulcers	Immune
ANA	Neurologic
Photosensitivity	



Radiographically, the arthritis of SLE is non-erosive (unlike RA).



Consider SLE in a patient who has involvement of 2 or more organ systems.

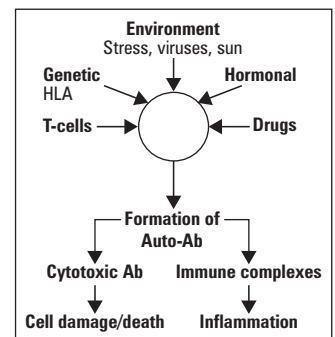


Figure 9. Multifactorial Etiology of SLE



Drug-Induced SLE

Often presents atypically with systemic features and serositis; usually associated with anti-histone antibodies.

**Raynaud's Phenomenon**

Vasospastic disorder characteristically causing discolouration of fingers and toes (white → blue → red).
Classic triggers: cold and emotional stress.

**Signs and Symptoms**

- characterized by periods of exacerbation and remission
- systemic
 - fatigue, malaise, weight loss, fever, lymphadenopathy
- vascular
 - Raynaud's phenomenon, livedo reticularis (mottled discolouration of skin due to narrowing of blood vessels, characteristic lacy or net-like appearance), thrombosis, vasculitis
- renal
 - glomerulonephritis, renal failure
- dermatologic
 - photosensitivity, malar rash, discoid rash, oral ulcers, alopecia (hair loss), purpura, panniculitis (inflammation of subcutaneous fat and muscle tissue), urticaria
- musculoskeletal
 - polyarthralgias, polyarthritis, myalgias, avascular necrosis
- ophthalmic
 - keratoconjunctivitis sicca, episcleritis, scleritis, cytoid bodies (cotton wool exudates on fundoscopy = infarction of nerve cell layer of retina)
- cardiac
 - pericarditis, coronary artery disease
- pulmonary
 - pleuritis, interstitial lung disease, pulmonary hypertension, PE, alveolar hemorrhage
- gastrointestinal
 - pancreatitis, lupus enteropathy, hepatitis, hepatomegaly
- neurologic
 - headache, depression, psychosis, seizures, cerebritis, transverse myelitis, peripheral neuropathy, stroke

Investigations

- ANA has high sensitivity (98%), but poor specificity → used as a screening test
- anti-dsDNA and anti-Sm are specific for SLE (95-99%)
- anti-dsDNA titer and serum complement (C3, C4) are useful to monitor treatment response in patients who are clinically and serologically concordant
 - anti-dsDNA increases and C3 and C4 decrease with disease activity
- anticardiolipin Ab and lupus anticoagulant in antiphospholipid antibody syndrome

Treatment

- principles of therapy
 - treat early and avoid long term steroid use, if possible
 - if high doses of steroids necessary for long-term control, add steroid sparing agents and taper when possible
 - treatment is tailored to organ system involved and severity of disease
 - all medications used to treat SLE require periodic monitoring for potential toxicity
- dermatologic
 - preventative: use sunscreen, avoid UV light and estrogens
 - topical steroids, hydroxychloroquine
- musculoskeletal
 - NSAIDs ± gastroprotective agent for arthritis (also beneficial for pleuritis and pericarditis)
 - hydroxychloroquine improves long term control and prevents flares
 - bisphosphonates, calcium, vitamin D to combat osteoporosis
- organ threatening disease
 - high-dose oral prednisone or IV methylprednisolone in severe disease
 - steroid sparing agents: azathioprine, methotrexate, mycophenolate
 - IV cyclophosphamide for serious organ involvement (e.g. cerebritis or SLE nephritis)

**Antiphospholipid Antibody Syndrome (APS)****Definition**

- multisystem vasculopathy manifested by recurrent thromboembolic events, spontaneous abortions and thrombocytopenia
- often presents with migraine type headaches
- circulating antiphospholipid autoantibodies interfere with coagulation cascade
- primary APS: occurs in the absence of other disease
- secondary APS: occurs in the setting of a connective tissue disease (including SLE), malignancy, drugs (hydralazine, procainamide, phenytoin, interferon, quinidine), and infections (HIV, TB, hepatitis C, infectious mononucleosis)
- catastrophic APS: development within 1 week of small vessel thrombotic occlusion in ≥3 organ systems with positive antiphospholipid antibodies (high mortality)

**Manifestations of APS**

Thromboembolic events
Spontaneous abortions
Thrombocytopenia

Table 10. Classification Criteria of APS: 1 clinical and 1 laboratory criteria must be present

Criteria	Description
Clinical	
Vascular thrombosis	Arterial: stroke/TIA, multi-infarct dementia, MI, valvular incompetence, limb ischemia Venous: DVT, PE, renal and retinal vein thrombosis Must be confirmed by imaging or histopathology
Pregnancy morbidity	Fetal death (> 10 wks GA), recurrent spontaneous abortions (< 10 wks GA) or premature birth (< 34 wks GA)
Laboratory	Labs must be positive on 2 occasions, at least 12 weeks apart
Lupus anticoagulant	
Anticardiolipin Ab	IgG and/or IgM
Anti-beta2 glycoprotein-I Ab	IgG and/or IgM

J Thromb Haemost 2006; 4:295–306

Signs and Symptoms

- see clinical criteria in Table 10
- hematologic
 - thrombocytopenia, hemolytic anemia, neutropenia
- skin
 - livedo reticularis, Raynaud's phenomenon, purpura, leg ulcers, and gangrene

Treatment

- thrombosis
 - lifelong anticoagulation with warfarin
 - target INR 2.0–3.0 for first venous event, >3.0 for recurrent and/or arterial event
- recurrent fetal loss
 - heparin/low molecular weight heparin ± aspirin during pregnancy
- catastrophic APS
 - high-dose steroids, anticoagulation, cyclophosphamide, plasmapheresis

A Systematic Review of Secondary Thromboprophylaxis in Patients with Antiphospholipid Antibodies

Arthritis Rheum 2007; 57:1487–95

Purpose: To systematically review the efficacy and safety data of different therapeutic approaches in patients with antiphospholipid antibodies (aPL) and thrombosis.

Study Selection: Randomized controlled trials, prospective and retrospective cohort studies, and subgroup analysis ($n > 15$) that focused on the secondary thromboprophylaxis in patients with aPL were selected.

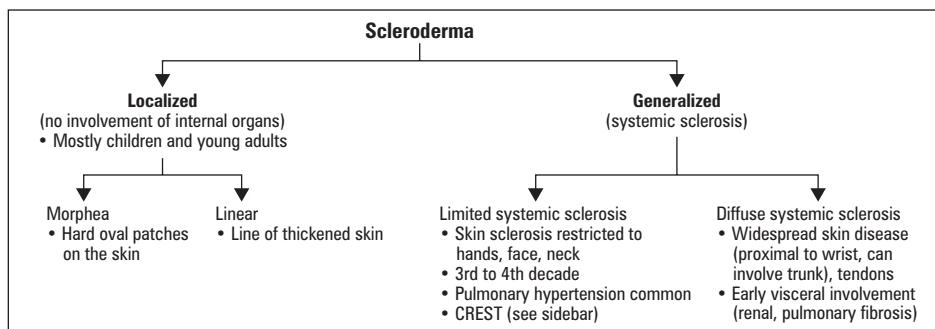
Results: Sixteen studies were selected. Patients with venous events and a single test for aPL showed a low recurrence rate while receiving oral anticoagulation at a target international normalized ratio (INR) of 2.0–3.0. Patients with stroke and a single positive aPL test had no increased risk compared with those without aPL. Recurrence rates in patients with definite antiphospholipid syndrome (APS) and previous venous thromboembolism were lower than in patients with arterial and/or recurrent events, both with and without therapy. Only 3.8% of recurrent events occurred at an actual INR >3.0. Mortality due to recurrent thrombosis was higher than mortality due to bleeding (18 patients versus 1 patient reported).

Conclusion: For patients with definite APS, the authors recommend prolonged warfarin therapy at a target INR of 2.0–3.0 in APS patients with first venous events and >3.0 for those with recurrent and/or arterial events. For patients with venous thromboembolism or stroke and a single positive aPL test, the authors recommend further testing to determine if they have a persisting antibody. If they do not, the same therapy as for the general population should be used (warfarin at a target INR of 2.0–3.0 and low-dose aspirin, respectively).

Scleroderma

Definition

- a non-inflammatory disorder characterized by widespread small vessel vasculopathy and fibrosis, which occurs in the setting of immune system activation and autoimmunity

**Figure 10. Forms of Scleroderma****Table 11. Classification Criteria of Systemic Sclerosis: 1 major or 2 minor criteria must be present**

Criteria	Description
Major	
Scleroderma proximal to MCPs	Skin tightness, thickening, non-pitting induration
Minor	
Sclerodactyly	Skin changes limited to digits
Digital pitting scars or loss of substance from finger pad	
Bibasilar pulmonary fibrosis	

American Rheumatism Association, 1980



CREST Syndrome

Calcinosis – calcium deposits on skin

Raynaud's phenomenon

Esophageal dysfunction – acid reflux

Sclerodactyly – tightening of skin on digits

Telangiectasia – superficial dilated blood vessels



Etiology and Pathophysiology

- idiopathic vasculopathy (not vasculitis) leading to atrophy and fibrosis of tissues
 - intimal proliferation and media mucinous degeneration → progressive obliteration of vessel lumen → fibrotic tissue
 - resembles malignant hypertension

Epidemiology

- F:M = 3-4:1, peaking in 5th and 6th decades
- associated with HLA-DR1
- associated environmental exposure (silica, epoxy resins, toxic oil, aromatic hydrocarbons, polyvinyl chloride)

Signs and Symptoms

Table 12. Clinical Manifestations of Scleroderma

System	Features
Dermatologic	Painless non-pitting edema → skin tightening Ulcerations, calcinosis, periungual erythema, hypo/hyperpigmentation, pruritus, telangiectasias Characteristic face: mask-like facies with tight lip, beak nose, radial perioral furrows
Vascular	Raynaud's phenomenon → digital pits, gangrene
Gastrointestinal (~90%)	Distal esophageal hypomotility → dysphagia Loss of lower esophageal sphincter function → GERD, ulcerations, strictures Small bowel hypomotility → bacterial overgrowth, diarrhea, bloating, cramps, malabsorption, weight loss Large bowel hypomotility → wide mouth diverticuli are pathognomonic radiographic finding on barium study
Renal	Mild proteinuria, creatinine elevation, hypertension "Scleroderma renal crisis" (10-15%) may lead to malignant arterial hypertension, oliguria and microangiopathic hemolytic anemia
Pulmonary	Interstitial fibrosis, pulmonary HTN, pleurisy, pleural effusions
Cardiac	Left ventricular dysfunction, pericarditis, pericardial effusion, arrhythmias
Musculoskeletal	Polyarthralgias "Resorption of distal tufts" (radiological finding) Proximal weakness 2° to disuse, atrophy, low grade myopathy
Endocrine	Hypothyroidism



Scleroderma is the most common cause of secondary Raynaud's phenomenon.



Lung disease is the most common cause of morbidity and mortality.

Investigations

- bloodwork
 - CBC, Cr, ANA
 - anti-topoisomerase 1/anti-Scl-70: specific but not sensitive for diffuse systemic sclerosis
 - anti-centromere: favours diagnosis of CREST variant (limited systemic sclerosis)
- imaging
 - CXR for fibrosis, echo for pulmonary HTN

Treatment

- dermatologic
 - good skin hygiene
 - low dose prednisone, methotrexate (limited evidence)
- vascular
 - patient education on cold avoidance
 - vasodilators (CCBs, local nitroglycerine cream, systemic PGE₂ inhibitors)
- gastrointestinal
 - GERD: PPIs are first line, then H₂-receptor agonists
 - small bowel bacterial overgrowth: broad spectrum antibiotics (tetracycline, metronidazole)
- renal disease
 - ACE inhibitors
- pulmonary
 - early interstitial disease: cyclophosphamide
 - pulmonary hypertension: vasodilators e.g. bosentan (Tracleer®), epoprostenol (Flolan®)
- cardiac
 - pericarditis: systemic steroids
- musculoskeletal
 - arthritis: NSAIDs, myositis: systemic steroids

Idiopathic Inflammatory Myopathy



Definition

- autoimmune diseases characterized by proximal muscle weakness \pm pain
- muscle becomes damaged by a non-suppurative lymphocytic inflammatory process
- classification
 - adult polymyositis (PM)/dermatomyositis (DM) (see Table 13)
 - juvenile DM (usually with vasculitis)
 - PM/DM associated with malignancy
 - ♦ increased risk of malignancy: age >50, DM>PM, normal CK, refractory disease
 - ♦ 2.4-6.5 fold increased risk of underlying malignancy usually in internal organs
 - PM/DM associated with connective tissue disease
 - inclusion body myositis (IBM)
 - ♦ age >50, M>F, slowly progressive, vacuoles in cells on biopsy
 - ♦ suspect when patient unresponsive to treatment
 - ♦ distal as well as proximal muscle weakness
 - ♦ muscle biopsy positive for inclusion bodies

POLYMYOSITIS (PM)/DERMATOMYOSITIS (DM)



Table 13. Classification Criteria for PM/DM. Definite if 4 present, probable if 3 present.

Criteria	Description
1. Symmetric proximal muscle weakness	Typical involvement of shoulders and hips
2. Elevated muscle enzymes	Increased CK, aldolase, LDH, AST, ALT
3. EMG changes	Short polyphasic motor units, high frequency repetitive discharge, insertional irritability
4. Muscle biopsy	Segmental fibre necrosis, basophilic regeneration, perivascular inflammation and atrophy
5. Typical rash of dermatomyositis	Required for diagnosis of DM (see below)

NEJM 1975; 292:403-7

Etiology and Pathophysiology

- PM is CD8 cell-mediated muscle necrosis, found in adults
- DM is β -cell and CD4 immune complex-mediated perifascicular vasculitis

Signs and Symptoms

- progressive symmetrical proximal muscle weakness (shoulder and hip) developing over weeks to months
 - difficulty lifting head off pillow, arising from chair, climbing stairs
- dermatological
 - DM has characteristic dermatological features (F>M, children and adults)
 - ♦ Gottron's papules
 - pink-violaceous, flat-topped papules overlying the dorsal surface of the interphalangeal joints
 - ♦ Gottron's sign
 - erythematous, smooth or scaly patches over the dorsal IPs, MCPs, elbows, knees, or medial malleoli
 - ♦ heliotropic rash: purple rash over the eyelids; usually with edema
 - ♦ shawl sign: erythematous rash over neck, upper chest, and shoulders
 - ♦ mechanic's hands: dark, dry, thick scale on palmar and lateral surface of digits
 - ♦ periungal erythema
- cardiac
 - dysrhythmias, CHF, conduction defect, ventricular hypertrophy, pericarditis
- gastrointestinal
 - oropharyngeal and lower esophageal dysphagia, reflux
- pulmonary
 - weakness of respiratory muscles, interstitial lung disease, aspiration pneumonia



Signs of DM
Gottron's papules and Gottron's sign are pathognomonic of DM (occur in 70% of patients).



Investigations

- bloodwork: CK, ANA, anti-Jo-1 (DM), anti-Mi-2, anti-SRP
- imaging: MRI may be used to localize biopsy site
- EMG, muscle biopsy

**Malignancies Associated with DM**

- Breast
- Lung
- Colon
- Ovarian

Treatment

- physical therapy and occupational therapy
- medical
 - high dose corticosteroid (1-2 mg/kg/day) and slow taper
 - add immunosuppressive agents (azathioprine, methotrexate, cyclosporine)
 - intravenous immunoglobulin for severe or refractory
 - hydroxychloroquine for DM rash
- malignancy surveillance
 - detailed history and physical (breast, pelvic and rectal exam)
 - CXR, abdominal and pelvic ultrasound, stool occult blood, Pap test, mammogram ± CT scan (thoracic, abdominal, pelvic)

Sjögren's Syndrome (SS)

Definition

- autoimmune condition characterized by dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia), caused by lymphocytic infiltration of salivary and lacrimal glands
- may evolve into systemic disorder with diminished exocrine gland activity in respiratory tract and skin
- primary and secondary form (associated with RA, SLE, DM and HIV)
- incidence estimated at 4/100,000 people
- 90% of cases are among females
- mean age of diagnosis is 40-60 yrs

Table 14. Classification Criteria for SS. Need 4 present, one of which includes salivary gland biopsy or autoantibodies

Criteria	Description
1. Dry eye symptoms	Dry >3 months, foreign body sensation, or requiring tear substitutes
2. Dry mouth symptoms	Dry >3 months, swollen salivary glands, or requiring liquids to swallow food
3. Dry eye signs	Schirmer test (to assess tear flow) or slit lamp exam with Rose Bengal stain
4. Dry mouth signs	Low salivary flow, sialography
5. Salivary gland biopsy	Focal lymphocytic sialoadenitis
6. Autoantibodies	anti-Ro and/or anti-La

Ann Rheum Dis 2002; 61:554-8

Signs and Symptoms

- "sicca complex": dry eyes (keratoconjunctivitis sicca), dry mouth (xerostomia)
- staphylococcus blepharitis
- dental caries, oral candidiasis, angular cheilitis (inflammation and fissuring at the commissures of the mouth)
- systemic complications
 - sinusitis, autoimmune thyroid dysfunction
 - arthralgias, arthritis
 - subclinical diffuse interstitial lung disease, xerotrachea leading to chronic dry cough
 - renal disease, glomerulonephritis
 - palpable purpura, vasculitis
 - peripheral neuropathy
 - lymphoma

Treatment

- ocular
 - artificial tears or surgical punctal occlusion for dry eyes
- oral
 - good dental hygiene, hydration
 - agents that stimulate salivary flow (e.g. pilocarpine)
 - topical nystatin or clotrimazole x 4-6 weeks for oral candidiasis
- systemic
 - hydroxychloroquine, corticosteroids, immunosuppressive agents

**Classic Triad (identifies 93% of Sjögren's patients)**

- Dry eyes
- Dry mouth (xerostomia) → dysphagia
- Arthritis (small joint, asymmetrical, nonerosive)



Patients with Sjögren's syndrome are at higher risk of non-Hodgkin's lymphoma.

Mixed Connective Tissue Disease (MCTD)/ Overlap Syndrome

- syndrome with features of 2 different CTD (e.g. SLE, scleroderma, PM)
- common symptoms: Raynaud's phenomenon, swollen fingers
- bloodwork: anti-RNP (see Table 19)
- prognosis
 - 50-60% will evolve into SLE
 - 40% will evolve into scleroderma
 - only 10% will remain as MCTD for the rest of their lives

Seropositive Rheumatic Disease: Vasculitides

- inflammation and subsequent necrosis of blood vessels leading to tissue ischemia or infarction
- any organ system can be involved
- keys to diagnosis
 - clinical suspicion: suspect in cases of unexplained multiple organ ischemia or systemic illness with no evidence of malignancy or infection
 - labs non-specific: anemia, increased WBC and ESR, abnormal urinalysis
 - biopsy if tissue accessible
 - angiography if tissue inaccessible
- treatment generally involves corticosteroids and/or immunosuppressives

Table 15. Classification of Vasculitis and Characteristic Features

Classification	Characteristic Features
SMALL VESSEL	
• Non-ANCA-associated	Immune complex mediated (most common mechanism)
Predominantly cutaneous vasculitis	Also known as hypersensitivity/leukocytoclastic vasculitis
Henoch-Schönlein purpura (see Pediatrics , P98)	Vascular deposition of IgA causing systemic vasculitis (skin, GI, renal), usually self-limiting, most common in childhood
Essential cryoglobulinemic vasculitis	Systemic vasculitis caused by circulating cryoproteins
• ANCA-associated	
Wegener's granulomatosis (c-ANCA > p-ANCA)	Granulomatous inflammation of vessels of respiratory tract and kidneys, initially have URTI symptoms, most common in middle age
Churg-Strauss syndrome (50% ANCA positive)	Granulomatous inflammation of vessels with hypereosinophilia and eosinophilic tissue infiltration, can be associated with p-ANCA or c-ANCA, other manifestations include coronary arteritis, myocarditis and neuropathy, average age 40's
Microscopic polyangiitis (70% ANCA positive, usually p-ANCA)	Pauci-immune necrotizing vasculitis, affecting kidneys (necrotizing glomerulonephritis), lungs (capillaritis and alveolar hemorrhage), skin. Most common in middle age
MEDIUM VESSEL	
Polyarteritis nodosa	Segmental non-granulomatous necrotizing inflammation. Unknown etiology in most cases, any age (average 40-50's), M > F
Kawasaki's (see Pediatrics , P98)	T-lymphocyte response and granuloma formation
LARGE VESSEL	
Giant cell arteritis (GCA) /Temporal Arteritis	Inflammation predominantly of the aorta and arteries originating from it. Over 50 years of age, F > M
Takayasu's arteritis	"Pulseless disease", chronic inflammation, most often the aorta and its branches. Usually young adults of Asian descent, F > M
OTHER VASCULITIDES	
Buerger's disease	Also known as thromboangiitis obliterans, inflammation secondary to pathological clotting, affects small and medium-sized vessels of distal extremities, may lead to distal claudication and gangrene, most important etiologic factor is cigarette smoking. Most common in young Asian males
Behçet's disease	Pathology: leukocytoclastic vasculitis, multisystem disorder presenting with ocular involvement, recurrent oral and genital ulceration, venous thrombosis, skin and joint involvement, more common in Mediterranean and Asia, average age 30's, M > F
Vasculitis mimicry	Cholesterol emboli, atrial myxoma



c-ANCA = circulating anti-neutrophil cytoplasmic antibody
p-ANCA = perinuclear anti-neutrophil cytoplasmic antibody



Features of Small Vessel Vasculitis

- Palpable purpura
- Vesicles
- Chronic urticaria
- Superficial ulcers



Churg-Strauss Triad

- Allergic rhinitis and asthma
- Eosinophilic infiltrative disease resembling pneumonia
- Systemic vasculitis



Features of Medium Vessel Vasculitis

- Livedo reticularis
- Erythema nodosum
- Raynaud's phenomenon
- Nodules
- Digital infarcts
- Ulcers

Predominantly Cutaneous Vasculitis

SMALL VESSEL NON-ANCA ASSOCIATED VASCULITIS

- subdivided into
 - drug-induced vasculitis
 - serum sickness reaction
 - vasculitis associated with other underlying primary diseases

Etiology and Pathophysiology

- cutaneous vasculitis following
 - drug exposure (allopurinol, gold, sulfonamides, penicillin, phenytoin)
 - viral or bacterial infection
 - idiopathic causes
- small vessels involved (post-capillary vessels most frequently)
- usually causes a leukocytoclastic vasculitis: debris from neutrophils around vessels
- sometimes due to cryoglobulins which precipitate in cold temperatures

Signs and Symptoms

- palpable purpura ± vesicles and ulceration, urticaria, macules, papules, bullae, subcutaneous nodules

Investigations

- vascular involvement (both arteriole and venule) established by skin biopsy

Treatment

- stop possible offending drug
- corticosteroids ± immunosuppressive agents
- usually self-limiting

Wegener's Granulomatosis

SMALL VESSEL ANCA-ASSOCIATED VASCULITIS

Definition

- granulomatous inflammation of vessels that may affect the upper airways (rhinitis, sinusitis), lungs (pulmonary nodules, infiltrates), and kidneys (glomerulonephritis, renal failure)
- highly associated with c-ANCA
- incidence 5 per 100,000; more common in Northern latitudes

Table 16. Classification Criteria: Wegener's diagnosed if 2 or more of the following 4 criteria present

Criteria	Definition
1. Nasal or oral involvement	Inflammation, ulcers, epistaxis
2. Abnormal findings on CXR	E.g. nodules, cavitations
3. Urinary sediment	Protein, RBC casts
4. Biopsy of involved tissue	Lungs show granulomas, kidneys show necrotizing segmental glomerulonephritis

American College of Rheumatology, 1990

Etiology and Pathophysiology

- transformation from inflammatory prodrome (serous otitis media and sinusitis) to full-blown vasculitic syndrome

Signs and Symptoms

- systemic
 - malaise, fever, weakness, weight loss
- ENT
 - sinusitis or rhinitis, nasal crusting and bloody nasal discharge, nasoseptal perforation, saddle nose deformity
 - inflammation/vasculitis involving extra-ocular muscles, retrobulbar space occupying lesions or direct extension of masses from the upper respiratory tract resulting in clinical finding of proptosis
 - hearing loss due to involvement of CN VIII
- pulmonary
 - cough, hemoptysis
- other
 - joint, skin, eye complaints, vasculitic neuropathy



Classic Features

- Necrotizing granulomatous vasculitis of lower and upper respiratory tract
- Focal segmental glomerulonephritis

Investigations

- bloodwork: anemia (normal MCV), increased WBC, increased Cr, increased ESR, ANCA (c-ANCA > p-ANCA)
- urinalysis: proteinuria, hematuria
- CXR: pneumonitis, lung nodules, infiltrations, cavitory lesions
- biopsy: renal (segmental necrotizing glomerulonephritis), lung (tracheobronchial erosion)
- possible decline in c-ANCA and ESR used to monitor response to treatment in some patients

Treatment

- prednisone 1 mg/kg/day PO for 3-6 months ± cyclophosphamide 2 mg/kg/day PO for 3-6 months followed by high dose methotrexate (20-25 mg PO/SC weekly) or azathioprine (2 mg/kg/day PO OD)
- consider biologic agents (infliximab, rituximab, IVIG) and plasmapheresis in systemic disease resistant to corticosteroids and cyclophosphamide

Polyarteritis Nodosa (PAN)

MEDIUM VESSEL VASCULITIS**Definition**

- pauci-immune necrotizing vasculitis of medium to small vessels, without associated glomerulonephritis or pulmonary capillaritis (as seen in microscopic polyangiitis)
- incidence 0.7 per 100,000; affects individuals between 40-60 yrs; M:F = 2:1

Table 17. Classification Criteria: PAN diagnosed if 3 or more of the following 10 criteria present

Criteria	Definition
1. Weight loss	>4 kg, not due to dieting or other factors
2. Myalgias, weakness or leg tenderness	Diffuse myalgias or weakness
3. Livedo reticularis	Mottled, reticular pattern over skin
4. Neuropathy	Mononeuropathy, multiple mononeuropathies or polyneuropathy
5. Testicular pain or tenderness	Not due to infection, trauma or other causes
6. Diastolic BP >90 mmHg	Development of hypertension with dBP >90 mmHg
7. Elevated Cr or BUN	Cr >1.5 mg/dL (132.6 µmol/L), BUN >40 mg/dL (14.3 mmol/L)
8. Hepatitis B positive	Presence of Hepatitis B surface antigen or antibody
9. Arteriographic abnormality	Commonly aneurysms
10. Biopsy of artery	Presence of granulocytes and / or mononuclear leukocytes in the artery wall

American College of Rheumatology, 1990

Etiology and Pathophysiology

- focal panmural necrotizing inflammatory lesions in small and medium-sized arteries
- thrombosis, aneurysm or dilatation at lesion site may occur
- healed lesions show proliferation of fibrous tissue and endothelial cells that may lead to luminal occlusion

Treatment

- prednisone 1 mg/kg/day PO and cyclophosphamide 2 mg/kg/day PO
- ± anti-viral therapy to enhance clearance of HBV



There is an association between Hepatitis B surface antigen (HBsAg) positivity and PAN.



Consider PAN in a non-diabetic patient with mononeuritis multiplex.

Giant Cell Arteritis (GCA)/Temporal Arteritis

LARGE VESSEL VASCULITIS**Table 18. Classification Criteria: GCA diagnosed if 3 or more of the following 5 criteria present**

Criteria	Definition
1. Age at onset >50	
2. New headache	
3. Temporal artery abnormality	Temporal artery tenderness or decreased pulse, not due to arteriosclerosis
4. Elevated ESR	ESR >50 mm/hour
5. Abnormal artery biopsy	Mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

American College of Rheumatology, 1990



GCA Criteria
Presence of 3 or more criteria yields sensitivity of 94%, specificity of 91%.

H**Medical Emergency**

Untreated, GCA can lead to permanent blindness in 20-25% of patients!

Signs and Symptoms

- temporal headaches ± scalp tenderness due to inflammation of involved portion of the temporal or occipital arteries
- sudden, painless loss of vision and/or diplopia due to narrowing of the ophthalmic or posterior ciliary arteries
- tongue and jaw claudication (pain in muscles of mastication on chewing)
- polymyalgia rheumatica (proximal myalgia, constitutional symptoms, elevated ESR) occurs in 30% of patients
- aortic arch syndrome (involvement of subclavian and brachial branches of aorta result in pulseless disease), aortic aneurysm ± rupture

Investigations

- diagnosis made by clinical suspicion, increased ESR, increased CRP, temporal artery biopsy within 14 days of starting steroids, angiography

Treatment

- if suspect GCA, immediately start high dose prednisone 1 mg/kg in divided doses, tapering prednisone as symptoms resolve; highly effective in treatment and in prevention of blindness and other vascular complications
- consider low dose ASA

Seropositive Rheumatic Disease: Investigations

Bloodwork, Urinalysis, Synovial Fluid Analysis

- general: CBC, BUN, creatinine
- acute phase reactants: complement (C3 and C4), fibrinogen, CRP, ferritin, albumin
- ESR increases with the increase of acute phase reactants, and chronically, with increase in gamma globulins
- C3, C4 often decrease in active SLE
- urinalysis to detect disease complications (proteinuria, active sediment)
- serology: autoantibodies (see Table 19)
- synovial fluid analysis (see Table 25)
- radiology (plain film, CT, MRI, ultrasound, bone densitometry, angiography, bone scan)

**Differential Diagnosis of Elevated ESR**

- RA, PMR, GCA
- Hypoalbuminemia, anemia, multiple myeloma
- Bacterial infections
- Malignancy

ESR (and CRP) is insensitive for PM/DM, AS, scleroderma, SLE, viral infections

Table 19. Autoantibodies and their Prevalence in Rheumatic Diseases

Autoantibody	Disease	Normal	Comments
RF	RA 80%	<5%	Autoantibodies (IgM>IgG>IgA) directed against Fc domain of IgG Present in most seropositive diseases Levels correlate with disease severity in RA Non-specific; may be present in IE, TB, Hep C, silicosis, sarcoidosis
	SS 50%	10-20%	
	SLE 20%	>65	
Anti-CCP	RA 80%		
ANA	SLE 98%	<5% other CTDs	Antibodies against nuclear components (DNA, RNA, histones, centromere) 1:40 dilution found in 5-30% of the normal population Sensitive but not specific for SLE
	MCTD 95%		
	SS 70-90%		
	CREST 80%		
Anti-dsDNA	SLE 50-70%	0%	Specific for SLE Levels correlate with disease activity
Anti-Sm	SLE <30%	0%	Specific but not sensitive for SLE
Anti-Ro (SSA)	SS 40-95%	0.5%	Subacute cutaneous SLE and mothers of babies with neonatal SLE 25%
Anti-La (SSB)	SS 40% SLE 10%	0%	Usually occurs with anti-Ro
Antiphospholipid antibodies (LAC, ACLA)	APS 100%	<5%	By definition present in APS Only small subset of SLE patients develop clinical syndrome of APS If positive will get a false positive VDRL test
	SLE 31-40%		
Anti-histone	Drug-induced SLE >90%	0%	
	Idiopathic SLE >50%	0%	
Anti-RNP	MCTD		Present in MCTD; present in many other CTD

Table 19. Autoantibodies and Their Prevalence in Rheumatic Diseases (continued)

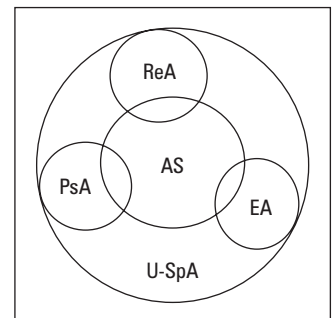
Autoantibody	Disease	Normal	Comments
Anti-centromere	CREST >80%	0%	Specific for CREST variant of systemic sclerosis
Anti-topoisomerase I (formerly Scl-70)	Diffuse systemic sclerosis 26-76%	0%	
c-ANCA	Active Wegener's >90%	0%	Specific and sensitive
p-ANCA	Wegener's 10% Other vasculitis	0%	Nonspecific and poor sensitivity (found in ulcerative colitis, polyarteritis nodosa, microscopic polyangiitis, Churg-Strauss, rapidly progressive glomerulonephritis)
Anti-Mi-2	DM 15-20%		Specific but not sensitive
Antibodies against RBCs, WBCs, or platelets	SLE		Perform direct Coomb's test Test hemoglobin, reticulocyte, leukocyte and platelet count, antiplatelet Abs

Seronegative Rheumatic Disease: Spondyloarthropathies

Table 20. A Comparison of the Spondyloarthropathies (inflammatory joint disease of the vertebral column)

Feature	AS	PsA	ReA	EA
M:F	5:1	1:1	8:1	1:1
Age of onset	20's	35-45	20's	Any
Peripheral arthritis	25%	96%	90%	Common
Distribution	Axial, LE	Any	LE	LE
Sacroiliitis	100%	40%	80%	20%
Dactylitis	Uncommon	Occasional	Common	Uncommon
Enthesitis	Common	Common	Common	Less Common
Skin lesions	Rare	100% Psoriasis	Common Keratoderma	Occasional Pyoderma, Erythema Nodosum
Uveitis	30%	Occasional	20%	Rare
Urethritis	Rare	Occasional	Common	Rare
Aortic Regurgitation	Occasional	Rare	Occasional	Occasional
HLA-B27	90%	40%	80%	30%

LE= Lower extremities

**Figure 11. Spondyloarthropathy Subsets**
(U-SpA = undifferentiated spondyloarthropathy)

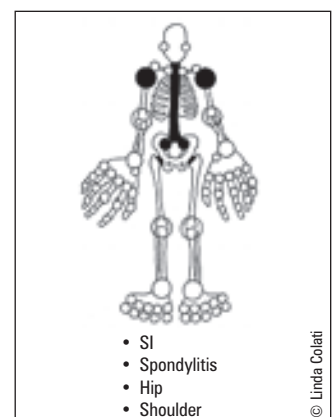
Ankylosing Spondylitis (AS)

Definition

- chronic inflammatory arthritis involving the sacroiliac joints and vertebrae (see Figure 12)
- prototype of the spondyloarthropathies

Table 21. Classification Criteria of AS: Definite AS if radiologic criterion and ≥1 clinical criterion are present. Probable AS if 3 clinical criteria alone or if the radiologic criterion is present

Criteria	Definition
Clinical	
1. Low back pain	>3 months, improved by exercise, but not relieved by rest
2. Limitation of lumbar spine motion	In both sagittal and frontal planes
3. Limitation of chest expansion	Relative to normal values for age and sex
Radiologic	
1. Sacroiliitis on radiographs	Sacroiliitis grade ≥2 bilaterally or grade 3-4 unilaterally

Modified New York Criteria, *Arthritis Rheum* 1984; 27:361**Figure 12. Common Sites of Involvement of AS**

**Rule of 2s****AS occurs in**

0.2% of the general population
2% of HLA-B27 positive individuals
20% of HLA-B27 positive individuals
with affected family member

Etiology and Pathophysiology

- enthesitis (inflammation of tendon or ligament at site of attachment to bone)
- inflammation → osteopenia → erosion → ossification → osteoproliferation (syndesmophytes)

Epidemiology

- M:F = 5:1; females have milder disease which may be under-recognized
- 95% of patients have HLA-B27 (9% HLA-B27 positive in general population)

Table 22. Types of Back Pain

Parameter	Mechanical	Inflammatory
Past History	±	++
Family History	–	+
Onset	Acute	Insidious
Age (years)	15-90	<40
Sleep Disturbance	±	++ (worse during 2nd half of night)
Morning Stiffness	<30 minutes	>1 hour
Involvement of Other Systems	–	+
Exercise	Worse	Better
Rest	Better	Worse
Radiation of Pain	Anatomic (L5-S1)	Diffuse (thoracic, buttock)
Sensory Symptoms	+	–
Motor Symptoms	+	–

Signs and Symptoms

- **axial**
 - mid and lower back stiffness, prolonged morning stiffness, night pain, persistent buttock pain, painful sacroiliac joint (+ Faber test) (see Table 22)
 - spinal restriction (decreased ROM): lumbar (decreased Schöber), thoracic (decreased chest wall expansion, normal >5 cm at T4), cervical (global decrease, often extension first)
 - postural changes: decreased lumbar lordosis + increased thoracic kyphosis + increased cervical flexion = increased occiput to wall distance
- **peripheral**
 - asymmetrical large joint arthritis, most often involving lower limb
 - enthesitis: tenderness over tibial tuberosity, or Achilles tendon and plantar fascia insertions into the calcaneum
- **extra-articular manifestations**
 - ophthalmic: acute anterior uveitis (25-30% patients)
 - renal: amyloidosis and IgA nephropathy
 - gastrointestinal: inflammatory bowel disease
 - cardiac: aortitis, aortic regurgitation, pericarditis, conduction disturbances, heart failure (rare)
 - respiratory: apical fibrosis (rare)
 - neurologic: cauda equina syndrome (rare)

**Extra-articular Manifestations of AS****6 As**

Atlanto-axial subluxation
Anterior uveitis
Apical lung fibrosis
Aortic incompetence
Amyloidosis (kidneys)
Autoimmune bowel disease (UC)



Consider AS in the differential for causes of aortic regurgitation.



The **Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)** is often used to measure and evaluate patient-reported disease activity in AS.

Investigations

- x-ray of SI joint: “pseudowidening” of joint due to erosion with joint sclerosis → bony fusion (late), symmetric sacroiliitis
- x-ray of spine: “squaring of edges” from erosion and sclerosis on corners of vertebral bodies leading to ossification of outer fibres of annulus fibrosis (bridging syndesmophytes) → “bamboo spine” radiographically
- MRI of spine: assess activity in early disease; detection of cartilage changes, bone marrow edema, bone erosions, and subchondral bone changes

Treatment

- **conservative/non-pharmacologic**
 - prevent fusion from poor posture and disability through: exercise (e.g. swimming), postural and deep breathing exercises, outpatient PT, smoking cessation
- **medical**
 - NSAIDs
 - glucocorticoids (topical eye drops, local injections)
 - DMARDs for peripheral arthritis (sulfasalazine, methotrexate)
 - biologics for axial and peripheral involvement
 - manage extra-articular manifestations
- **surgical**
 - hip replacement, vertebral osteotomy for marked deformity

Prognosis

- spontaneous remissions and relapses are common and can occur at any age
- function may be excellent despite spinal deformity
- favourable prognosis if female and age of onset >40 years
- early onset with hip disease may lead to severe disability; may require arthroplasty

Enteropathic Arthritis (EA)

- see *Gastroenterology, Inflammatory Bowel Disease, G19*
- manifestations of ulcerative colitis (UC) and Crohn's disease (CD) include peripheral arthritis (large joint, asymmetrical), spondylitis, and hypertrophic osteoarthropathy
- arthralgia, myalgia, osteoporosis and aseptic necrosis of bone 2° to steroid treatment of bowel inflammation
- NSAIDs should be used cautiously as they may exacerbate bowel disease



Both AS and EA feature symmetric sacroiliitis.

Table 23. Comparing Features of Spondylitis vs. Peripheral Arthritis in EA

Parameter	Spondylitis	Peripheral Arthritis
HLA-B27 association	Yes	No
Gender	M>F	M=F
Onset before IBD	Yes	No
Parallels IBD course	No	Yes
Type of IBD	UC = CD	CD

Psoriatic Arthritis (PsA)**Etiology and Pathophysiology**

- unclear but many genetic, immunologic and some environmental factors involved (e.g. psoriatic plaque flora, particularly Group A *Streptococcus*, and trauma)

Epidemiology

- psoriasis affects 1% of population
- arthropathy in 10% of patients with psoriasis
- 15-20% of patients will develop joint disease before skin lesions appear

Signs and Symptoms

- **dermatologic**
 - well-demarcated erythematous plaques with silvery scale
 - nail involvement: pitting, transverse or longitudinal ridging, discolouration, subungual hyperkeratosis, onycholysis and oil drops
- **musculoskeletal**
 - 5 general patterns
 - ♦ asymmetric oligoarthritis (most common – 70%)
 - ♦ arthritis of DIP joints with nail changes
 - ♦ destructive (mutilans) arthritis (5%)
 - ♦ symmetric polyarthritis (similar to RA)
 - ♦ sacroiliitis and spondylitis (usually older, male patients)
 - other findings: dactylitis, enthesopathy
- **ophthalmic**
 - conjunctivitis, iritis (uveitis)
- **cardiac and respiratory** (late findings)
 - aortic insufficiency
 - apical lung fibrosis
- **neurologic**
 - cauda equina syndrome
- **radiologic**
 - floating syndesmophytes
 - pencil in cup appearance at IP joints
 - osteolysis, periostitis

Treatment

- treat skin lesions (e.g. steroid cream, salicylic and/or retinoic acid, tar, UV light)
- NSAIDs or intra-articular steroids
- DMARDs, biologic therapies to minimize erosive disease (use early if peripheral joint involvement)



Check "hidden" areas for psoriatic lesions (ears, hair line, umbilicus, gluteal cleft, nails).

Risks and Benefits of Tumour Necrosis Factor-alpha Inhibitors in the Management of Psoriatic Arthritis: Systematic Review and Meta-analysis of Randomized Controlled Trials

J Rheumatol 2008; 35:883-90

Purpose: To evaluate the efficacy and safety of tumour necrosis factor-alpha (TNF-alpha) inhibitors in the management of psoriatic arthritis (PsA).

Study Selection: Randomized controlled trials (RCT) of adalimumab, etanercept, and infliximab used in patients with PsA.

Results: Six RCT met the inclusion criteria, including 982 patients. All 3 TNF-alpha inhibitors were significantly more effective than placebo on the basis of Psoriatic Arthritis Response Criteria (PsARC) and American College of Rheumatology response criteria ACR20, ACR50, and ACR70 ratings. There were no significant differences between TNF-alpha inhibitors and placebo in the proportions of patients who withdrew for any reason (RR 0.48, 95% CI 0.20-1.18), or withdrawal due to adverse events (RR 2.14, 95% CI 0.73-6.27), serious adverse events (RR 0.98, 95% CI 0.55-1.77), or upper respiratory tract infections (RR 0.91, 95% CI 0.65-1.28). Pooled rates for injection site reactions were significantly higher for adalimumab and etanercept than for placebo (RR 2.48, 95% CI 1.16-5.29), but there was no significant difference in the proportion of patients experiencing infusion reactions with infliximab (RR 1.03, 95% CI 0.48-2.20) compared to placebo. Indirect analysis did not demonstrate any significant differences between the TNF-alpha inhibitors.

Conclusions: TNF-alpha inhibitors are effective treatments for PsA with no important added risks associated with their short-term use. There is still a need for longterm risk-benefit assessment of using these drugs for the management of PsA.

Reactive Arthritis (ReA)

Definition

- two meanings
 1. reactive arthritis: a sterile arthritis following an infection (e.g. rheumatic fever, post viral arthritis etc.)
 2. Reactive Arthritis (ReA): formerly known as Reiter's Syndrome; one of the seronegative spondyloarthropathies in which patients have a peripheral arthritis (of ≥ 1 month duration) accompanied by one or more extra-articular manifestations that appears shortly after certain infections of the GI or GU tracts

Etiology

- onset following an infectious episode either involving the GI or GU tract
 - GI: *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia* species
 - GU: *Chlamydia* (isolated in 16-44% of ReA cases), *Mycoplasma* species
- acute clinical course
 - 1-4 weeks post-infection
 - lasts weeks to years with 1/3 chronic
 - often recurring
 - spinal involvement persists

Epidemiology

- in HLA-B27 patients, axial > peripheral involvement
- M>F

Signs and Symptoms

- **musculoskeletal**
 - peripheral arthritis, asymmetric pattern, spondylitis (thick and skipped syndesmophytes), Achilles tendinitis, plantar fasciitis, dactylitis
- **ophthalmic**
 - iritis (anterior uveitis), conjunctivitis
- **dermatologic**
 - keratoderma blenorrhagicum (hyperkeratotic skin lesions on palms and soles) and balanitis circinata (small, shallow, painless ulcers of glans penis and urethral meatus) are diagnostic
- **gastrointestinal**
 - oral ulcers, diarrhea
- **urethritis and cervicitis**
 - sterile cultures; presence not related to site of initiating infection

Investigations

- diagnosis is clinical plus laboratory
- bloodwork: normocytic, normochromic anemia and leukocytosis; sterile cultures
- serology: HLA-B27 positive

Treatment

- antibiotics for non-articular infections
- NSAIDs, physical therapy, exercise
- local therapy
 - joint protection
 - intra-articular steroid injection
 - topical steroid for ocular involvement
- systemic therapy
 - corticosteroids, sulfasalazine, methotrexate (for peripheral joint involvement only)
 - TNF inhibitors for spinal inflammation



Look for genetic predisposition (HLA-B27) and infection.



"Can't see, can't pee, can't climb a tree":
Triad of conjunctivitis, urethritis and arthritis is 99% specific (but 51% sensitive) for ReA.

Crystal-Induced Arthropathies

Table 24. Gout vs. Pseudogout

Parameter	Gout	Pseudogout
Gender	M>F	M=F
Age	Middle-aged males Post-menopausal females	Older
Onset of disease	Acute	Acute/insidious
Crystal type	Monosodium urate (MSU) Negative birefringence (yellow when parallel), needle-shaped	Calcium pyrophosphate dihydrate (CPPD) Positive birefringence (blue when parallel), rhomboid-shaped
Distribution	First MTP	Knee, wrist, polyarticular
Radiology	"Holes in bones"	Chondrocalcinosis OA (knee, wrist, 2nd and 3rd MCP)
Treatment	NSAIDs, corticosteroids, colchicine, allopurinol	NSAIDs, corticosteroids

Gout

Definition

- derangement in purine metabolism resulting in hyperuricemia; monosodium urate crystal deposits in tissues (tophi) and synovium (microtophi)

Etiology and Pathogenesis

- sources of uric acid: diet and endogenous
- synthesis
 - hypoxanthine → xanthine → uric acid
 - both steps catalyzed by xanthine oxidase

Hyperuricemia

- primary or genetic**
 - mostly due to idiopathic renal underexcretion (90%)
 - also idiopathic overproduction or abnormal enzyme production/function
- secondary**
 - dietary excess
 - underexcretion (>90%) – renal failure, drugs, systemic conditions
 - overproduction (<10%) – increased nucleic acid turnover states (e.g. malignancy, post-chemotherapy)
- sudden changes in uric acid concentration are more important than absolute values
 - changes in pH, temperature or initiation of antihyperuricemics may precipitate an acute gouty attack
- common precipitants: alcohol, dietary excess, dehydration (e.g. thiazide and loop diuretics), trauma, illness, surgery
- other associated conditions: hypertension, obesity, diabetes, starvation

Epidemiology

- most common in males >45 years old
- extremely rare in premenopausal female

Signs and Symptoms

- recurrent episodes of acute inflammatory arthritis
- acute gouty arthritis**
 - severe pain, redness, joint swelling, usually involving lower extremities (see Figure 13)
 - joint mobility may be limited
 - attack will subside spontaneously within several days to weeks; may recur
- tophi**
 - urate deposits on cartilage, tendons, bursae, soft tissues, and synovial membranes
 - common sites: first MTP, ear helix, olecranon bursae, tendon insertions (common in Achilles tendon)
- kidney**
 - gouty nephropathy
 - uric acid calculi

Investigations

- joint aspirate: >90% of joint aspirates show crystals of monosodium urate (see Table 24) (negatively birefringent, needle-shaped)
- x-rays may show tophi as soft tissue swelling, punched-out lesions

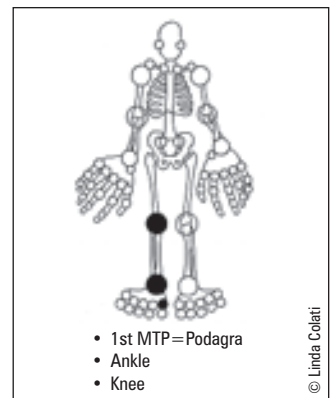


Figure 13. Common Sites of Involvement in Gout (asymmetric joint involvement)



An acute gout attack may mimic cellulitis. However, joint mobility is preserved in cellulitis.



Precipitants of Gout

Drugs are FACT

Furosemide
Aspirin/Alcohol
Cytotoxic drugs
Thiazide diuretics

Foods are SALTS

Shellfish
Anchovies
Liver and Kidney
Turkey
Sardines



The majority of people with hyperuricemia do not have gout, and normal or low uric acid levels do not rule out gout

Treatment

- **acute gout**
 - NSAIDs: high dose, then taper as symptoms improve
 - corticosteroids: intra-articular, oral or intra-muscular (if renal, cardiovascular or GI disease and/or if NSAIDs contraindicated or failed)
 - colchicine within first 24 hours but effectiveness limited by narrow therapeutic range
 - allopurinol can worsen an acute attack (**therefore do not start during acute flare**)
- **chronic gout**
 - conservative
 - ♦ avoid foods with high purine content (e.g. visceral meats, sardines, shellfish, beans, peas)
 - ♦ avoid drugs with hyperuricemic effects (e.g. pyrazinamide, ethambutol, thiazide, alcohol)
 - medical
 - ♦ antihyperuricemic drugs (allopurinol and febuxostat): decrease uric acid production by inhibiting xanthine oxidase
 - ♦ uricosuric drugs (probenecid, sulfinpyrazone): use if failure on or intolerant to allopurinol; do not use in renal failure
 - prophylaxis prior to starting antihyperuricemic drugs (colchicine/low-dose NSAID)
 - in renal disease secondary to hyperuricemia, use low-dose allopurinol and monitor creatinine

Pseudogout

Etiology and Pathophysiology

- acute inflammatory arthritis due to phagocytosis of IgG-coated calcium pyrophosphate dihydrate (CPPD) crystals by neutrophils and subsequent release of inflammatory mediators within joint space

Epidemiology

- more frequently polyarticular, slower in onset in comparison to gout, lasts up to 3 weeks but is self-limited
- risk factors: old age, advanced OA, neuropathic joints
- other associated conditions: hyperparathyroidism, hypothyroidism, hypomagnesemia, hypophosphatasia (low ALP), diabetes, hemochromatosis

Signs and Symptoms

- affects knees, wrists, MCPs, hips, shoulders, elbows, ankles, big toe (see Figure 14)
- episodes of acute inflammatory arthritis
- may present as chronic arthritis with acute exacerbations
- 5% will mimic rheumatoid arthritis (symmetrical polyarticular pattern with morning stiffness and constitutional symptoms)
- may be triggered by dehydration, acute illness, surgery, trauma
- 50% of the patients will develop degenerative joint changes

Investigations

- must aspirate joint to rule out septic arthritis, gout
- CPPD crystals: present in 60% of patients, often only a few crystals
- x-rays show chondrocalcinosis in 75%: radiodensities in fibrocartilaginous structures (e.g. knee menisci) or linear radiodensities in hyaline articular cartilage

Treatment

- joint aspiration, rest, and protection
- NSAIDs – also used for maintenance therapy
- prophylactic colchicine PO (controversial)
- intra-articular or oral steroids to relieve inflammation

Synovial Fluid Analysis

- synovial fluid is an ultrafiltrate of plasma plus hyaluronic acid; it lubricates joint surfaces and nourishes articular cartilage

Three Most Important Tests of Synovial Fluid (3 C's)

1. Cell count and differential
 2. Culture and Gram stain (bacteria, mycobacteria, fungi)
 3. Crystal examination (microscopy with polarized light)
 - gout (monosodium urate) → needle-shaped, negatively birefringent (yellow)
 - pseudogout (calcium pyrophosphate dihydrate) → rhomboid-shaped, positively birefringent (blue)
- chemistry – protein, LDH, glucose less helpful

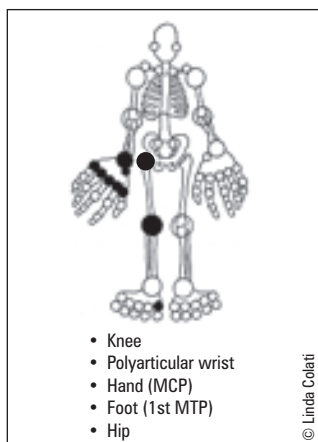


Figure 14. Common Sites of Involvement in CPPD

Table 25. Synovial Fluid Analysis

Parameter	Normal	Non-Inflammatory	Inflammatory	Infectious	Hemorrhagic
Colour	Clear	Clear	Opaque	Opaque	Sanguinous
Viscosity	High (due to hyaluronic acid)	High	Low	Low	Variable
WBC/mm ³	<200	<2,000	>2,000	>50,000	Variable
% PMN	<25%	<25%	>25%	>50%	Variable
Examples		Trauma Osteoarthritis Neuropathy Hypertrophic – arthropathy	Seropositives Seronegatives Crystal arthropathies	Septic arthritis	Trauma Hemophilia

Pediatric Rheumatology

- see [Pediatrics](#), P95

Non-Articular Rheumatism

Definition

- disorders that primarily affect soft tissues or periarticular structures
- includes bursitis, tendinitis, tenosynovitis, fibromyalgia and polymyalgia rheumatica

Polymyalgia Rheumatica (PMR)



Definition

- characterized by profound pain and stiffness of the proximal extremities (girdle area)
- closely related to giant cell arteritis (15% of patients with PMR develop GCA)
- no muscle weakness

Table 26. Headley's Diagnostic Criteria: All of the following are required for diagnosis of PMR

1. Age >50 at onset
2. Pain for >1 month in at least 2 of the following 3 areas: neck, shoulders or pelvic girdle
3. Increased ESR (>40 mm/h)
4. Rapid response to corticosteroids (<20 mg/day of prednisolone)
5. Must rule out other potential causes (e.g. infection, RA, SLE, PAN, polymyositis, malignancy)

Semin Arthritis Rheum 1984; 13:322-8

Epidemiology

- incidence 50 per 100,000 per year in those over age 50
- age of onset typically >50, F:M = 2:1

Signs and Symptoms

- constitutional symptoms prominent (fever, weight loss, malaise)
- pain and stiffness of symmetrical proximal muscles (neck, shoulder and hip girdles, thighs), gel phenomenon (stiffness after prolonged activity)
- physical examination reveals tender muscles but no weakness or atrophy

Investigations

- bloodwork: often shows anemia, elevated platelets, ESR and CRP; normal CK

Treatment

- goal of therapy: symptom relief
- start with steroid dose of 15-20 mg PO daily
- taper slowly over 2-year period monitoring ESR and symptoms closely
- treat relapses aggressively (50% relapse rate)



PMR Criteria

1. Age >50
2. Bilateral aching/morning stiffness >1 month
3. ESR >40 mm/hr
4. Prompt response to low-dose corticosteroids

Prednisone Plus Methotrexate for Polymyalgia Rheumatica: A Randomized, Double-blind, Placebo-controlled Trial

Ann Intern Med 2004; 141:493-500

Study: Multicenter randomized, double-blind, placebo-controlled trial.

Patients: Patients with newly diagnosed polymyalgia rheumatica.

Intervention: Prednisone dosage (25 mg/d) was tapered to 0 mg/d within 24 weeks and was adjusted if flare-ups occurred. Oral methotrexate (10 mg) or placebo, with folic acid supplementation (7.5 mg), was given weekly for 48 weeks.

Primary Outcome: The proportion of patients no longer taking prednisone, the number of flare-ups, and the cumulative prednisone dose after 76 weeks.

Results: Twenty-eight of 32 patients in the methotrexate group and 16 of 30 patients in the placebo group were no longer taking prednisone at 76 weeks ($P = 0.003$). The risk difference was 34 percentage points (95% CI, 11 to 53 percentage points). Similar results were obtained after adjustment for C-reactive protein level and duration of symptoms in a multivariate model. Fifteen of 32 patients in the methotrexate group and 22 of 30 patients in the placebo group had at least 1 flare-up by the end of follow-up ($P = 0.04$). The median prednisone dose was 2.1 g in the methotrexate group and 2.97 g in the placebo group ($P = 0.03$). The rate and severity of adverse events were similar.

Limitations: Follow-up was short, and a high dose of folic acid and a relatively high starting dosage of prednisone were used. Ten of 72 patients (14%) discontinued treatment or were lost to follow-up.

Conclusions: Prednisone plus methotrexate is associated with shorter prednisone treatment and steroid sparing. It may be useful in patients at high risk for steroid-related toxicity.



Fibromyalgia

Definition

- chronic, widespread pain with characteristic tender points

Table 27. Classification Criteria for Fibromyalgia: Need criterion 1 and 2. Note, the presence of another clinical disorder does not exclude the diagnosis of fibromyalgia

1. History of widespread pain	At least 3 months in 4 quadrants of the body
2. Pain in $\geq 11/18$ tender point sites	With approximate force of 4 kg by digital palpation See location of tender points in Figure 15

Arthritis Rheum. 1990;33:160-72.

A 14-week, Randomized, Double-Blinded, Placebo-Controlled Monotherapy Trial of Pregabalin in Patients With Fibromyalgia

J Pain 2008; Jun 2

Study: Multicentre, randomized, double-blinded, placebo-controlled trial.

Patients: Patients ($n=750$) meeting American College of Rheumatology criteria for fibromyalgia and who had a pain score of at least 40 mm on the 100-mm pain visual analog scale (VAS).

Intervention: Patients were randomly assigned to placebo or pregabalin (300 mg/d, 450 mg/d, or 600 mg/d) given twice daily in equally divided doses for 12 weeks.

Primary Outcome: Change in the mean pain score derived from the subject's daily pain diary as measured at the patient's baseline to the end point of the study.

Results: Patients in 2 pregabalin treatment groups (450 and 600 mg/d pregabalin) showed a statistically significant improvement in the end point mean pain score compared with placebo-treated subjects (mean difference, -0.50; $P = .0147$ [450 mg/d] and -0.45, $P = .0287$ [600 mg/d]). The $\approx 30\%$ responder rate was 30% (56/184) in the placebo arm and 42% (76/183) in the 300 mg/d, 50% (94/190) in the 450 mg/d, and 48% (88/188) in the 600 mg/d pregabalin arms ($P = .0172$, $P = .0002$, $P = .0006$, respectively), whereas the $\approx 50\%$ responder rate was 15% (28/184) for placebo, 24% (44/183) for 300 mg/d, 27% (52/190) for 450 mg/d, and 30% (57/188) for 600 mg/d ($P = .0372$, $P = .0038$, $P = .0010$, respectively). The number needed to treat (NNT) for the $\approx 30\%$ response rate was 9.01 for 300 mg/d, 5.25 for 450 mg/d, and 5.73 for 600 mg/d. The NNT for the $\approx 50\%$ responder rate was 11.33 for 300 mg/d, 8.23 for 450 mg/d, and 6.62 for 600 mg/d. Discontinuations due to adverse events were 12%, 16%, 22%, and 26% in placebo and pregabalin 300, 450, and 600 mg/d groups, respectively. The 450 and 600 mg/d groups were significantly different from placebo ($P = .0001$).

Conclusions: Pregabalin at 300 mg/d, 450 mg/d, and 600 mg/d showed statistically significant response rates as compared to placebo although discontinuation rates for the 450 mg/d and 600 mg/d regimens were significantly higher as compared to placebo.

Exercise for Treating Fibromyalgia Syndrome

Cochrane Database Syst Rev 2007; 4:CD003786

Study: Cochrane systematic review of 34 randomized controlled trials.

Population: 2276 patients diagnosed with fibromyalgia.

Intervention: Exercise training including cardiorespiratory endurance, muscle strengthening, and flexibility.

Primary Outcome: Global well-being, selected signs and symptoms, and physical function.

Result: Aerobic-only exercises improve global well-being, physical function, and possibly pain and tender points. There was insufficient data to evaluate the effect of strength and flexibility on the primary outcomes.

Conclusions: Moderate aerobic cardiorespiratory exercise improves function and well-being in patients with FM. Benefits from strength and flexibility require additional research to delineate benefits.

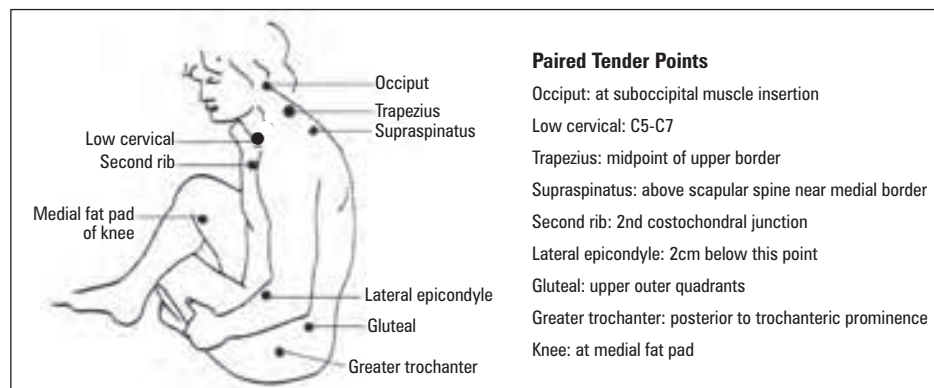


Figure 15. Characteristic Tender Points in Fibromyalgia

Epidemiology

- F:M = 3:1
- primarily ages 25-45, some adolescents
- prevalence of 2-5% in general population
- overlaps with chronic fatigue syndrome and myofascial pain syndrome
- strong association with psychiatric illness

Signs and Symptoms

- widespread aching, stiffness and reproducible tender points (see Figure 15)
- easy fatigability
- sleep disturbance: non-restorative sleep, difficulty falling asleep, and frequent waking
- symptoms aggravated by physical activity, poor sleep, emotional stress
- patient feels that joints are diffusely swollen although joint examination is normal
- neurologic symptoms of hyperalgesia, paresthesias
- associated with irritable bowel or bladder syndrome, migraines, tension headaches, restless legs syndrome, obesity, depression, and anxiety

Investigations

- bloodwork: includes TSH and ESR; all typically normal unless underlying illness present
- serology: do not order ANA or RF unless there is clinical suspicion for a connective tissue disease
- laboratory sleep assessment

Treatment

- conservative**
 - education
 - exercise program (walking, aquatic exercises), physical therapy (good posture, stretching, muscle strengthening, massage)
 - stress reduction, CBT
 - biofeedback, meditation, acupuncture may be helpful
- medical**
 - low dose tricyclic antidepressant (e.g. amitriptyline)
 - for sleep restoration
 - select those with lower anticholinergic side effects
 - SNRI: duloxetine, milnacipran
 - anticonvulsant: pregabalin
 - analgesics may be beneficial for pain that interferes with sleep

Common Medications

Table 28. Common Medications for Osteoarthritis

Class	Generic Drug Name	Trade Name	Dosing (PO)	Indications	Contraindications	Adverse Effects
	acetaminophen	Tylenol®	500 mg tid	1st line		Hepatotoxicity Overdose >10 g Potentiates warfarin
NSAIDs	ECASA		325-975 mg qid	2nd line	GI bleed Renal impairment Allergy to ASA, NSAIDs Pregnancy (T3)	Nausea, tinnitus, vertigo, rash, dyspepsia, GI bleed, PUD, hepatitis, renal failure, HTN, nephrotic syndrome
	ibuprofen	Advil®, Motrin®	200-600 mg tid			
	diclofenac	Voltaren®	25-50 mg tid			
	diclofenac/misoprostol	Arthrotec®	50-75/200 mg tid			
	naproxen	Naprosyn®, Aleve®	125-500 mg bid			
	meloxicam	Mobicox®	7.5-15 mg OD			
COX-2 Inhibitors	celecoxib	Celebrex®	200 mg OD	High risk for GI bleed: age >65 hx of GI bleed, PUD	Renal impairment Sulfa allergy (celecoxib) Cardiovascular disease	Delayed ulcer healing Renal/hepatic impairment Rash
Other treatments		Comments				
Combination analgesics (acetaminophen + codeine)		Enhanced short term effect compared to acetaminophen alone More adverse effects: sedation, constipation, nausea, GI upset				
Intra-articular corticosteroid injection		Short-term (weeks-months) decrease in pain and improvement in function				
Intra-articular hyaluronic acid q6months		Modest decrease in pain Used for mild-moderate OA of the knees Precaution with chicken/egg allergy				
Topical NSAIDs		1.5% wt/wt topical diclofenac (Pennsaid®) May use for patients who fail acetaminophen treatment and who wish to avoid systemic therapy				
Capsaicin cream		Mild decrease in pain				
Glucosamine sulfate ± chondroitin		Limited clinical studies No regulation by Health Canada				

Table 29. Disease Modifying Anti-Rheumatic Drugs (DMARDs)

Generic Drug Name	Trade Name	Dosing	Contraindications	Adverse Effects
COMMONLY USED				
hydroxychloroquine \$	Plaquenil®	400 mg PO OD initially 200-400 mg PO OD maintenance	Retinal disease, G6PD deficiency	GI symptoms, macular damage, neuromyopathy, skin rash
sulfasalazine \$	Salazopyrim® Azulfidine® (US)	1000 mg PO bid-tid	Sulfa/ASA allergy, kidney disease, G6PD deficiency	GI symptoms, headache, leukopenia, rash
methotrexate \$	Rheumatrex® Folex/Mexate®	7.5-25 mg PO/IM/SC qweekly	Bone marrow suppression, liver disease, significant lung disease, immunodeficiency, pregnancy, EtOH abuse	Urticaria, GI symptoms, tubular necrosis, myelosuppression, cirrhosis, pneumonitis, oral ulcers
leflunomide \$\$	Arava®	10-20 mg PO OD	Liver disease	Alopecia, GI symptoms, pulmonary infiltrates, liver dysfunction
NOT COMMONLY USED				
cyclosporine \$\$	Neoral®	2.5-3 mg/kg/d divided and given in 2 doses PO	Kidney/liver disease, infection, hypertension	Bleeding, hypertension, decreased renal function, hair growth, tremors
gold (injectable) \$	Solganal® Mycrysine®	10 mg IM q1week increasing to response	IBD, kidney/liver disease	Rash, mouth soreness/ulcers, proteinuria, marrow suppression
azathioprine \$	Imuran®	1-2/5 mg/kg/d PO OD	Kidney/liver disease TPMT deficiency	Pancytopenia, biliary stasis, rash, hair loss, vomiting, diarrhea
cyclophosphamide \$	Cytoxan®	1 g/m ² /month IV as per protocol	Kidney/liver disease	Cardiotoxicity, GI symptoms, hemorrhagic cystitis, nephrotoxicity, bone marrow suppression, sterility

Table 29. DMARDs (continued)

Generic Drug Name	Trade Name	Dosing	Mechanism of Action
NEWER DMARDs (Biologics)			
etanercept \$\$\$	Enbrel®	25 mg biweekly or 50 mg weekly SC	Fusion protein of TNF receptor and Fc portion of IgG
infliximab \$\$\$	Remicade®	3-5 mg/kg IV q 8 weeks	Chimeric mouse/human monoclonal anti-TNF-alpha
anakinra \$\$\$	Kineret®	100 mg SC OD	Interleukin-1 receptor antagonist
adalimumab \$\$\$	Humira®	40 mg SC q 2 weeks	Monoclonal anti-TNF-alpha
abatacept \$\$\$	Orencia®	IV infusion	Costimulation modulator of T-cell activation
rituximab \$\$\$	Rituxan®	2 IV infusions, 2 weeks apart	Causes B-cell depletion, binds to CD20
certolizumab \$\$\$	Cimzia®	400 mg SC q 2 weeks x3 then 200 mg SC q 4 weeks	PEGylated monoclonal anti-TNF-alpha
golimumab \$\$\$	Simponi®	50 mg SC q month	Monoclonal anti-TNF-alpha
tocilizumab \$\$\$	Actemra®	4-8 mg/kg IV q 4 weeks	Interleukin-6 receptor antagonist

References

- ACR. Guidelines for the Medical Management of Osteoarthritis of the Hip — 11/95.
 ACR. Guidelines for the Medical Management of Osteoarthritis of the Knee — 11/95.
 ACR. Guidelines for Referral and Management of Systemic Lupus Erythematosus in Adults — 9/99.
 ACR Subcommittee on Rheumatoid Arthritis Guidelines, 2002. Guidelines for the Management of Rheumatoid Arthritis: 2002 Update.
 Alattah D, Neogi T, Silman AJ, et al. 2010 Rheumatoid Arthritis Classification Criteria. *Arthritis and Rheumatism* 2010;62(9):2569-2581
 Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
Arthritis & Rheumatism 46(2):328-346.
 Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *NEJM* 2000;343:1586-93.
 Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *NEJM* 1975;292:403-7.
 Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. The VIGOR Study Group. *NEJM* 2000;343:1520-28.
 Bookman AM. Clinical Evaluation of Arthritis. University of Toronto Foundations of Medical Practice Lecture. 2006.
 Brady OH, Masri BA, Garbuz DS, Duncan CP. 10. Joint replacement of the hip and knee — when to refer and what to expect. *CMAJ* 2000;163(10):1285-91.
 Brater DC, Harris C, Redfern JS, Gertz BJ. Renal effects of COX-2-selective inhibitors. *Amer J Nephrol* 2001;21(1):1-15.
CMAJ Clinical Basics Rheumatology Series.
 Cibere J. 4. Acute monoarthritis. *CMAJ* 2000;162(11):1577-83.
 Clark BM. 9. Physical & occupational therapy in the management of arthritis. *CMAJ* 2000;163(8):999-1005.
 Ensworth S. 1. Is it arthritis? *CMAJ* 2000;162(7):1011-6.
 Healey LA. Long-term follow-up of polymyalgia rheumatica: evidence for synovitis. *Semin Arthritis Rheum* 1984;13:322-8.
 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. *Arthritis Rheum* 1997;40:1725.
 Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990;33:1122-8.
 Huang SHK. 7. Basics of therapy. *CMAJ* 2000;163(4):417-23
 Klippel JH, Weyand CM, and Wortmann RL. *Primer on Rheumatic Diseases*, 11th ed. Arthritis Foundation, 1997.
 Klinkhoff A. 5. Diagnosis and management of inflammatory polyarthritis. *CMAJ* 2000;162(13):1833-38.
 Kremer, JM. Rational use of new and existing disease-modifying agents in rheumatoid arthritis. *Ann Intern Med* 2001;134: 695-706.
 Lacaille D. 8. Advanced therapy. *CMAJ* 2000;163(6):721-8.
 Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum* 1990;33:1101-7.
 Lightfoot RW Jr, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990;33:1088-93.
 Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295-306.
Musculoskeletal Injury; (OPOT). Queen's Printer of Ontario, June 2000. www.opot.org
 Ontario Musculoskeletal Therapeutics Review Panel. Ontario Treatment Guidelines for Osteoarthritis, Rheumatoid Arthritis, and Acute Price GE. 6. Localized therapy. *CMAJ* 2000;163(2):176-83.
 Puttick MPE. 11. Evaluation of the patient with pain all over. *CMAJ* 2001;164(2):223-27.
 Reid G, Esdaile JM. 3. Getting the most out of radiology. *CMAJ* 2000;162(9):1318-25.
 Shojania K. 2. What laboratory tests are needed? *CMAJ* 2000;162(8):1157-63.
 Smetana, GW and Shmerling RH. Does this patient have temporal arteritis? *JAMA* 2002; 287:92-101.
 Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980;23:581-90.
 Taunton F, Wilkinson M. 14. Diagnosis and management of anterior knee pain. *CMAJ* 2001;164(11):1595-601.
 Tsang I. 12. Pain in the neck. *CMAJ* 2001;164(8):1182-7.
 Van der Linden. A proposal for modification of the New York criteria. *Arthritis Rheum*, 1984; 27:361.
 Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61:554-8.
 Wade, J.P. 15. Osteoporosis. *CMAJ* 2001;165(1):45-50.
 Wing PC. 13. Minimizing disability in patients with low-back pain. *CMAJ* 2001;164(19):1459-68.
 Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. *Arthritis Rheum* 1990; 33:160-72.

Samir Bidnur, Yonah Krakowsky and Deborah Sasges, chapter editors

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Basic Anatomy Review

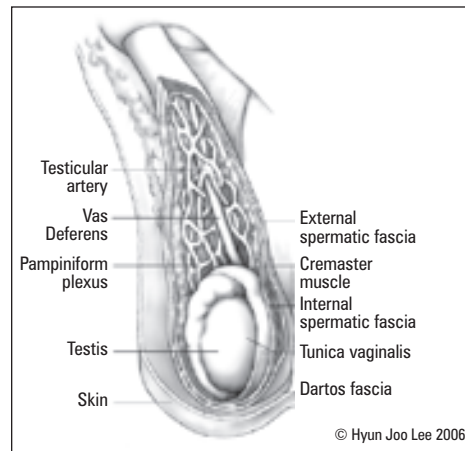
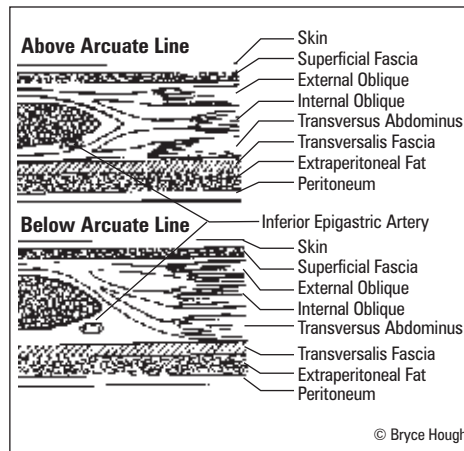
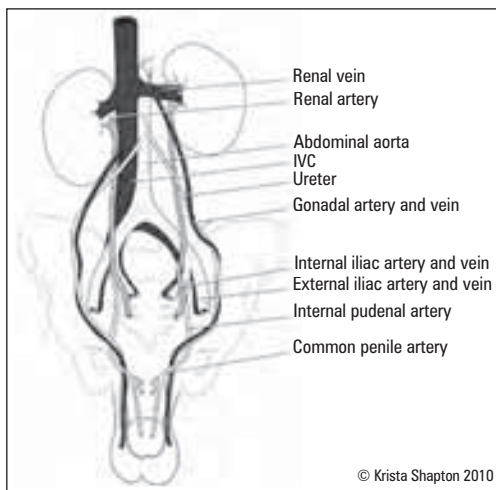


Figure 1. Midline Cross-Section of Abdominal Wall

Figure 2. Anatomy of Scrotum



Male Pelvic Vasculature

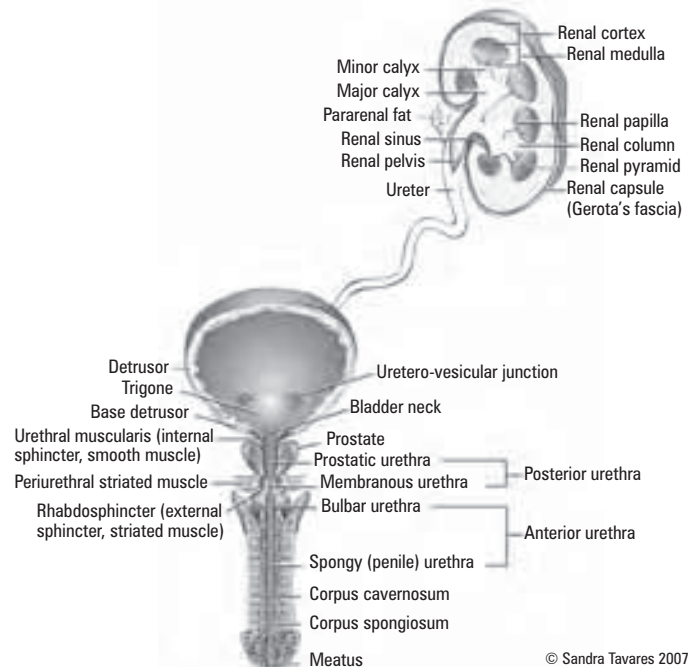


Figure 3. Essential Genito-Urinary Tract Anatomy

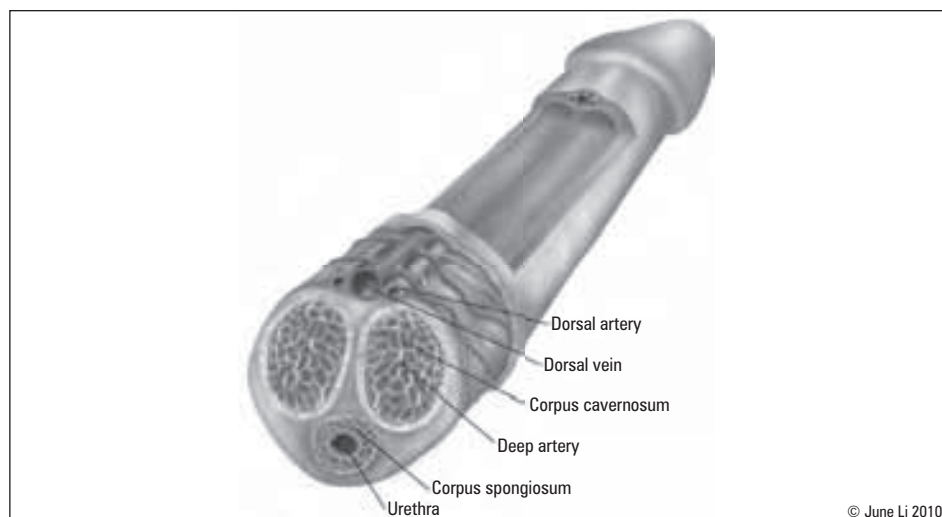


Figure 4. Cross Section of the Penis

Common Presenting Problems

Hematuria



Classification (see [Nephrology](#), NP6)

Table 1. Etiology of Hematuria by Age Group

Age (years)	Etiology (in order of decreasing frequency)	
0-20	Glomerulonephritis, UTI, congenital anomalies	
20-40	UTI, stones, bladder tumour	
40-60	Male: bladder tumour, stones, UTI	Female: UTI, stones, bladder tumour
>60	Male: BPH, bladder tumour, UTI	Female: bladder tumour, UTI

Etiology

Table 2. Etiology of Hematuria by Type

Pseudohematuria	Pre-renal	Renal	Post-renal
Vaginal bleeding	Anticoagulants	Stone	Stone
Dyes (beets, rhodamine B in candy and juices)	Coagulation defects	Trauma	Tumour
Hemoglobin (hemolytic anemia)	Sickle cell disease	Renal cell carcinoma	Cystitis
Myoglobin (rhabdomyolysis)	Neoplasms	Transitional cell carcinoma	Urethritis
Drugs (rifampin, phenazopyridine, pyridium, phenytoin)	Leukemia	Wilm's tumour	Polyps
Porphyrria	Thromboembolism	Pyelonephritis	Foreign body
Laxatives (phenolphthalein)		Glomerulonephritis	Urethral stricture
		Interstitial nephritis	
		Tuberculosis	
		Infarct	
		Polycystic kidneys	
		Arteriovenous malformation	



Common urologic causes of hematuria can be grossly classified as:

Trauma
Infection
Tumours
Stones



Gross painless hematuria is bladder cancer until proven otherwise.

History

- full history, inquire about timing of macroscopic hematuria in urinary stream
 - initial: anterior urethra
 - terminal: bladder neck and prostatic urethra
 - total: bladder and/or above

Investigations

- gross hematuria and symptomatic hematuria require full workup
 - CBC (rule out anemia, leukocytosis), electrolytes, creatinine, BUN
 - urine studies:
 - urinalysis (casts, crystals, cells)
 - culture and sensitivity
 - cytology
 - imaging:
 - CT/IVP to investigate upper tracts (ultrasound alone is not sufficient)
 - cystoscopy to investigate lower tract (possible retrograde pyelogram)
- microscopic hematuria defined as more than two red blood cells (RBC) per high-power field (HPF) (see Figure 5)

Acute Management of Severe Bladder Hemorrhage

- manual irrigation via catheter with normal saline to remove clots
- continuous bladder irrigation (CBI) using large (22-26 Fr) 3-way Foley to help prevent clot formation
- cystoscopy if bleeding quite active:
 - identify resectable tumours
 - coagulate obvious sites of bleeding
- refractory bleeding:
 - continuous intravesical irrigation with 1% alum (aluminum potassium sulfate) solution as needed
 - intravesical instillation of 1% silver nitrate solution
 - intravesical instillation of 1-4% formalin (need general anesthesia)
 - embolization or ligation of iliac arteries
 - cystectomy and diversion rarely



The CUA guidelines advise: Repeat initial urine microscopy if history of urethral trauma, exercise, or menses. Immediate referral to nephrology if any of: proteinuria, ↑ creatinine, red cell casts or dysmorphic RBCs



Upper Tract Imaging Options

Intravenous Pyelogram – Traditional option and widely available, but use is decreasing. Reasonable sensitivity for UCC, but poor sensitivity for RCC.

Ultrasound – Superior to IVP for evaluation of renal parenchyma and renal cysts. Limited sensitivity for UCC and small renal masses. U/S alone is not sufficient for upper tract imaging.

CT – Optimal test for renal parenchyma, calculi and infections, but less available and more expensive than ultrasound. Involves exposure to radiation and intravenous contrast.

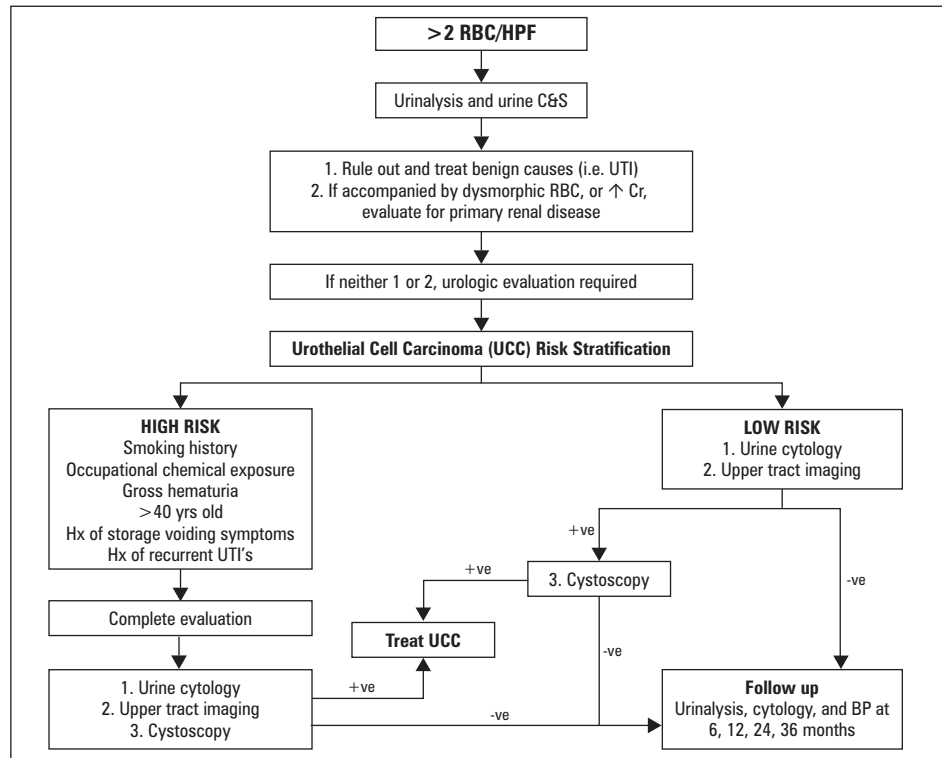


Figure 5. Workup of Asymptomatic Microscopic Hematuria Based on AUA Guidelines

Scrotal Complaints

- see *Scrotal Mass*, U27

Urinary Retention

- see *Failure to Void*, U6

Dysuria

Differential Diagnosis

Table 3. Differential Diagnosis of Dysuria

Infectious	Cystitis, urethritis, prostatitis, epididymitis, orchitis, cervicitis, vulvovaginitis, perineal inflammation/infection, TB, vestibulitis
Neoplasm	Renal cell, bladder, prostate, penis, vagina/vulva, BPH
Calculi	Bladder stone, ureteral stone, kidney stone
Inflammatory	Seronegative arthropathies (reactive arthritis: arthritis, uveitis, urethritis), drug side effects, autoimmune disorders, chronic pelvic pain syndrome (CPPS), interstitial cystitis
Hormonal	Endometriosis, hypoestrogenism
Trauma	Catheter insertion, post-coital cystitis (honeymoon cystitis)
Psychogenic	Somatization disorder, MDD, stress/anxiety disorder
Other	Contact sensitivity, foreign body

Approach

- focused history and physical to determine cause (fever, discharge, CVA tenderness, conjunctivitis, back/joint pain)
- urine dip, C&S, R&M
- any discharge (urethral, vaginal, cervical) should be sent for gonococcus/chlamydia testing; wet mount if vaginal discharge
- if suspect infection, may start empiric antibiotic treatment
- ± imaging of urinary tract (tumour, stones)

Voiding Dysfunction

- see Gynecology, GY36 for relevant female topics

Voiding

- two phases of lower urinary tract function:
 1. Storage phase – bladder filling and urine storage
 - ♦ accommodation and compliance
 - ♦ no involuntary contraction
 2. Voiding phase – bladder emptying
 - ♦ coordinated detrusor contraction
 - ♦ synchronous relaxation of outlet sphincters
 - ♦ no anatomic obstruction
- voiding dysfunction can therefore be classified as:
 - failure to store – due to bladder or outlet
 - failure to void – due to bladder or outlet
- three types of symptoms: storage (formerly known as irritative), voiding (formerly known as obstructive), post-void

Failure to Store: Urinary Incontinence

Definition

- involuntary leakage of urine

Etiology

- urgency incontinence:
 - detrusor overactivity:
 - ♦ CNS lesion, inflammation/infection (cystitis, stone, tumour), bladder neck obstruction (tumour, stone), BPH
 - decreased compliance of bladder wall:
 - ♦ CNS lesion, fibrosis
 - ♦ sphincter/urethral problem
- stress urinary incontinence (SUI):
 - urethral hypermobility
 - ♦ weakened pelvic floor allows bladder neck and urethra to descend with increased intra-abdominal pressure
 - ♦ urethra is pulled open by greater motion of posterior wall of outlet relative to anterior wall
 - ♦ associated with childbirth, pelvic surgery, aging, levator muscle weakness
 - intrinsic sphincter deficiency (ISD)
 - ♦ pelvic surgery, neurologic problem, aging and hypoestrogen state
 - intrinsic sphincter deficiency and urethral hypermobility can co-exist

Epidemiology

- variable prevalence in women: 25-45%
- F:M = 2:1
- more frequent in the elderly, affecting 5-15% of those living in the community and 50% of nursing home residents

Table 4. Urinary Incontinence: Types and Treatments

Type	Urge	Stress	Overflow	Mixed
Definition	Involuntary leakage of urine preceded by a strong, sudden urge to void	Involuntary leakage of urine with sudden increases in intra-abdominal pressure	Involuntary leakage of urine when intravesical pressure exceeds urethral pressure	Urinary leakage associated with urgency and increased intra-abdominal pressure
Etiology	Bladder (detrusor overactivity)	Urethra/Sphincter weakness, post-partum pelvic musculature weakness	Obstruction, neuropathy (diabetes, MS, anticholinergic drugs)	Combination of bladder and sphincter issues
Diagnosis	History Urodynamics	History Stress Test (have patient bear down/cough)	History Urodynamics	History Urodynamics Stress Test



Failure to Store Lower Urinary Tract Symptoms (LUTS) (irritative)

- Frequency
- Urgency
- Nocturia
- Dysuria

Think

Frequent Urgent Nighttime Discomfort



Causes of Reversible Urinary Incontinence

DIAPERS

Delirium
Inflammation/Infection
Atrophic vaginitis/urethritis
Pharmaceuticals/Psychological
Excess urine output
Restricted mobility/Retention
Stool impaction

**Urge Incontinence Treatment**

Beware of anticholinergic side effects including delirium and urinary retention.

Table 4. Urinary Incontinence: Types and Treatments (continued)

Type	Urge	Stress	Overflow	Mixed
Treatment	Lifestyle Bladder habit training Botox Medications: <i>Anticholinergics</i> (tolterodine (Detrol®), oxybutynin (Ditropan®), trospium (Trosec®), solifenacin (Vesicare®), TCA's Neuromodulation	Weight loss, Kegel's exercises Bulking agents Surgery (slings, TVOT, artificial sphincters)	Lifestyle Catheterization to avoid organ damage Treat underlying cause	Combination of management of urge and stress incontinence

**Failure to Void: Urinary Retention****Acute vs. Chronic Retention**

Acute retention is a medical emergency characterized by pain and anuria with normal bladder volume and architecture. Acute overdistention can lead to bladder rupture.

Chronic retention can be asymptomatic with greatly increased bladder volume and detrusor hypertrophy followed by atony (late).

Etiology

- outflow obstruction:
 - bladder neck or urethra – calculus, clot, foreign body, or neoplasm
 - prostate – BPH, prostate cancer, prostatitis
 - urethra – stricture, phimosis, traumatic disruption
- bladder innervation:
 - spinal cord – injury, disc herniation, multiple sclerosis
 - stroke
 - DM
 - post-pelvic surgery
- pharmacologic:
 - anticholinergics
 - narcotics
 - antihypertensives (ganglionic blockers, methyldopa)
 - over-the-counter cold medications containing ephedrine or pseudoephedrine (e.g. Sudafed®)
 - antihistamines (e.g. Benadryl®, Nytol®, Somnex®)
 - psychosomatic substances (e.g. ecstasy)

Clinical Features

- palpable and/or percussible bladder (suprapubic)
- possible purulent/bloody meatal discharge
- DRE – size of prostate, anal sphincter tone
- neurological – presence of abnormal deep tendon reflexes, “anal wink”, saddle sensation, etc.

Investigations

- CBC, electrolytes, Cr, BUN, urine R&M, C&S, ultrasound, cystoscopy, urodynamic studies, post void residual (PVR) scan

Treatment

- guiding principles are to treat underlying cause of retention and use least invasive treatment possible
- catheterization:
 - contraindicated in trauma patient unless urethral disruption has been ruled out
 - acute retention: immediate catheterization to relieve retention, leave Foley in to drain bladder, follow up to determine cause
 - chronic retention: intermittent catheterization by patient is commonly used; definitive treatment depends on etiology
- suprapubic cystostomy
- for post-operative patients with retention:
 - encourage ambulation
 - alpha-blockers to relax bladder neck
 - may need catheterization
 - definitive treatment will depend on etiology

Benign Prostatic Hyperplasia (BPH)

Definition

- hyperplasia of stroma and epithelium in periurethral area of prostate (transition zone) – see Figure 6
- tone of prostatic smooth muscle cells plays a role in addition to hyperplasia

Etiology

- etiology unknown
 - androgen dihydrotestosterone (DHT) required (converted from testosterone by 5- α reductase)
 - possible role of impaired apoptosis, estrogens, other growth factors

Epidemiology

- age-related, extremely common (50% of 50 year olds, 80% of 80 year olds)
- 25% of men will require treatment

Clinical Features

- result from outlet obstruction and compensatory changes in detrusor function
- voiding symptoms:
 - hesitancy, straining, weak/interrupted stream, incomplete bladder emptying
 - decreased flow rates may be seen on uroflowmetry
 - due to outflow obstruction and/or impaired detrusor contractility
- storage symptoms:
 - urgency, frequency, nocturia, urgency incontinence
 - thought to be due to detrusor overactivity and decreased compliance
- prostate is smooth, rubbery and symmetrically enlarged on DRE
- complications:
 - retention
 - overflow incontinence
 - hydronephrosis and renal compromise
 - infection
 - gross hematuria
 - bladder stones

Investigations

- history
 - assess LUTS and effect on quality of life, may include self-administered questionnaires (AUA symptom and impact score)
- physical exam: DRE
- urinalysis to exclude UTI
- creatinine to assess renal function \pm renal ultrasound to assess for hydronephrosis
- prostate-specific antigen (PSA) to rule out malignancy (if life expectancy >10 years)
- uroflowmetry to measure flow rate (optional)
- bladder ultrasound to determine post-void residual urine (optional)
- cystoscopy prior to potential surgical management
- biopsy if suspicious for malignancy

Treatment

- conservative for those with mild symptoms:
 - watchful waiting – 50% of patients improve spontaneously
 - includes lifestyle changes (e.g. evening fluid restriction, planned voiding)
- medical treatment:
 - α -adrenergic antagonists – reduce stromal smooth muscle tone [e.g. terazosin (Hytrin[®]), doxazosin (Cardura[®]), tamsulosin (Flomax[®]), alfuzosin (Xatral[®])]
 - 5- α reductase inhibitor – blocks conversion of testosterone to DHT; acts on the epithelial component of the prostate – reduces prostate size [e.g. finasteride (Proscar[®]), dutasteride (Avodart[®])]
 - combination shown to be synergistic (see sidebar)
- transurethral resection of prostate (TURP):
 - see *Selected Urological Procedures*, U40
- open prostatectomy:
 - for large prostates or associated problems (e.g. bladder stones)
 - suprapubic (transvesically to deal with bladder pathology)
 - retropubic (through the prostatic capsule)
- minimally invasive therapy:
 - prostatic stents, microwave therapy, laser ablation, water-induced thermotherapy, cryotherapy, high intensity focused ultrasound (HIFU) and transurethral needle ablation (TUNA)

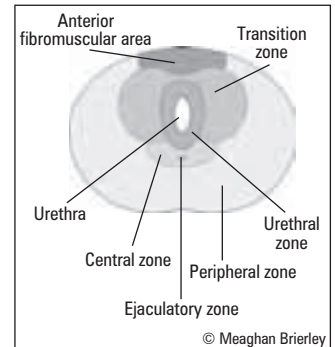


Figure 6. Cross-Section of Prostate



AUA Prostate Symptom Score FUNWISE

Frequency
Urgency
Nocturia
Weak stream
Intermittency
Straining
Emptying, incomplete feeling of

Each symptom graded out of 5.
0-7 – Mildly symptomatic
8-19 – Moderately symptomatic
20-35 – Severely symptomatic

Note: Dysuria not included in score but is commonly associated with BPH



Prostate size does not correlate well with symptoms in BPH.



Approximate Prostate Sizes

20 cc – chestnut
25 cc – plum
50 cc – lemon
75 cc – orange
100 cc – grapefruit



Absolute Indications for BPH Surgery

- Refractory urinary retention
- Recurrent UTIs
- Recurrent hematuria refractory to medical treatment
- Renal insufficiency (rule out other causes)
- Bladder stones



Urethral Stricture

The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia (Medical Therapy of Prostatic Symptoms (MTOPS) Trial)

NEJM 2003; 349:2387-2398

Study: Randomized, double-blinded, controlled trial with mean follow-up of 4.5 years.

Patients: 3047 patients with symptomatic BPH (AUA symptom score 8 to 35) were randomly assigned to placebo (n=737), doxazosin (n=756), finasteride (n=768), or combination therapy (n=786). Mean age 62.6.

Intervention: Conservative treatment vs. doxazosin vs. finasteride vs. combination therapy.

Main Outcomes: Clinical progression defined as: first occurrence of an increase over base line of at least four points in the AUA symptom score, acute urinary retention, renal insufficiency, recurrent urinary tract infection, or urinary incontinence.

Results: The 6-yr absolute reduction in cumulative incidence of clinical progression of symptomatic BPH compared to placebo for doxazosin was 39% (P<0.001), finasteride was 34% (P=0.002), and combination therapy was 66% (P<0.001). Combination therapy was more effective than either doxazosin (P<0.001) or finasteride (P<0.001) alone. There was no significant difference between doxazosin and finasteride alone.

Conclusion: Long-term combination therapy with doxazosin and finasteride reduced the risk of overall clinical progression of benign prostatic hyperplasia significantly more than did treatment with either drug alone.

Definition

- decrease in urethral calibre due to scar formation in urethra (may also involve corpus spongiosum)
- M>F

Etiology

- congenital – failure of normal canalization
 - may cause bilateral hydronephrosis
- trauma:
 - instrumentation (most common)
 - external trauma (e.g. burns, straddle injury)
 - other: foreign body, removal of inflated Foley catheter, etc.
- infection:
 - long-term indwelling catheter
 - balanitis xerotica obliterans (lichen sclerosis or chronic progressive sclerosing dermatosis of the male genitalia) causes meatal stenosis

Clinical Features

- voiding symptoms (obstructive symptoms)
- urinary retention
- related infections: recurrent UTI, secondary prostatitis/epididymitis

Investigations

- laboratory findings
 - flow rates <10 ml/s (normal ~20 ml/s) on uroflowmetry
 - urine culture usually negative, but may show pyuria
- radiologic findings
 - retrograde urethrogram, voiding cystourethrogram (VCUG) will demonstrate location
- urethroscopy

Treatment

- urethral dilatation:
 - temporarily increases lumen size by breaking up scar tissue
 - healing will often reform scar tissue and recreate stricture
- visual internal urethrotomy (VIU):
 - endoscopically incise stricture without skin incision
 - cure rate 50-80% with single treatment, <50% with repeated courses
- open surgical reconstruction:
 - complete stricture excision ± anastomosis, ± urethroplasty depending on location and size of stricture

Neurogenic Bladder

Definition

- a malfunctioning urinary bladder due to a deficiency in some aspect of its innervation

Neurophysiology

Table 5. Efferent Sympathetic, Parasympathetic, and Somatic Nerve Supply

Nerve Fibres	Segment	Neurotransmitter	Target	Key Receptors
Sympathetic	T10-L2	Noradrenaline	Trigone, internal sphincter, proximal urethra	Adrenergic (α 1)
Somatic	S2-S4	Acetylcholine	External sphincter	Nicotinic
Parasympathetic	S2-S4	Acetylcholine	Detrusor	Muscarinic (M2, M3)

- receptors in the bladder wall and mucosa relay information to pontine micturition centre (PMC) and activate micturition reflex
- the PMC sends excitatory/inhibitory signals to regulate micturition reflex (normally inhibited by cortical input)
 - micturition: stimulation of sacral parasympathetic neurons (bladder contraction); inhibition of sympathetic (IS relaxation) and sacral somatic neurons (ES relaxation)
 - urine storage: inhibition of sacral parasympathetic neurons (bladder relaxation) aided by sympathetic activation (bladder relaxation, IS contraction); stimulation of sacral somatic neurons (ES contraction)
- voluntary action of external sphincter (pudendal n. S2-S4) can inhibit urge to urinate
- cerebellum, basal ganglia, thalamus, and hypothalamus all have input at PMC



4Cs of Bladder

Capacity (350-500 cc;

Peds: (Age + 2) x 30)

Compliance (minimal Δ Pressure/ Δ Volume)

Contractility (voluntary and sustained)

Cooperation of bladder and sphincter



Nerve roots in micturition:

“S2-3-4 keeps the urine off the floor.”

Classification of Neurologic Voiding Dysfunction

- lesion above PMC [e.g. stroke, tumour, multiple sclerosis (MS)]: neurogenic detrusor overactivity (detrusor hyperreflexia)
 - loss of voluntary inhibition of voiding
 - intact pathway inferior to PMC maintains coordination of voiding episodes
- lesion of spinal cord [e.g. MS, arteriovenous malformation (AVM)]: detrusor sphincter dyssynergia (DSD)
 - loss of coordination between detrusor and sphincter (i.e. detrusor contracts on closed sphincter and vice versa)
 - component of detrusor overactivity as well
- lesion of sacral cord or peripheral efferents (e.g. trauma, diabetes, disc herniation): detrusor atony/areflexia
 - flaccid bladder which fails to contract
 - may progress to poorly compliant bladder with high pressures
- peripheral autonomic neuropathy: deficient bladder sensation → increasing residual urine → decompensation (e.g. DM, neurosyphilis, herpes zoster)
- muscular lesion: can involve detrusor, smooth/striated sphincter



"Spinal shock" early phase following cord injury manifests as atonic bladder.

Neuro-Urologic Evaluation

- history and physical exam (urologic and general neurologic)
- urinalysis, renal profile
- imaging: intravenous pyelogram (IVP), U/S to rule out hydronephrosis and stones
- cystoscopy
- urodynamic studies:
 - uroflowmetry – assess flow rate, pattern
 - filling cystometrogram (CMG) – assess capacity, compliance, detrusor overactivity
 - voiding cystometrogram – pressure-flow study, assess bladder contractility and extent of bladder outflow obstruction
 - EMG – helps ascertain presence of coordinated or uncoordinated voiding, allows accurate diagnosis of DSD
 - video study – x-ray contrast to visualize bladder/bladder neck/urethra during CMG

Treatment

- goals of treatment:
 - maintenance of low pressure storage and emptying system with minimal tubes and collecting devices is necessary to
 - ♦ prevent renal failure
 - ♦ prevent infections
 - ♦ prevent incontinence or achieve social continence
- treatment options: depends on status of bladder and urethra
 - bladder hyperactivity → medications to relax bladder (see *Incontinence*, U5)
 - ♦ if refractory:
 - botulinum toxin injections into bladder wall
 - occasionally augmentation cystoplasty
 - flaccid bladder → clean intermittent catheterization (CIC)

Autonomic Dysreflexia

- exaggerated sympathetic nervous system response to visceral stimulation below the lesion in spinal cord injury patients
 - lesion is usually above T6/T7
 - stimulation includes instrumentation, distention or stimulation of bladder, urethra or rectum
- symptoms include: hypertension, headache, reflex bradycardia, sweating, anxiety, piloerection
- vasoconstriction below lesion, vasodilation above lesion
- treatment: remove noxious stimulus (e.g. insert catheter), parenteral ganglionic or α -blockers, nifedipine (prophylaxis during cystoscopy)

Post Obstructive Diuresis (POD)

Definition

- polyuria resulting from relief of severe chronic obstruction
- $>3\text{ L}/24\text{ hrs}$ or $>200\text{ cc/hr}$ over each of **two consecutive hours**

Pathophysiology

- ranges in severity: physiologic to pathologic process
 - **physiologic POD** occurs secondary to excretion of retained urea, sodium, and water (high osmotic load) after relief of obstruction
 - ♦ self-limiting, usually resolves in 48 hrs with PO fluids but sometimes can continue even after having reached euvolemic status (i.e. pathologic POD)

- **pathologic POD** is a sodium-wasting nephropathy that occurs secondary to an impaired concentrating ability of the renal tubules due to:
 - ♦ decreased reabsorption of sodium chloride in the thick ascending limb and urea in the collecting tubule
 - ♦ increased medullary blood flow (solute washout)
 - ♦ increased flow and solute concentration in the distal nephron

Management

- admit patient and closely monitor hemodynamic status and electrolytes
- monitor urine output (U/O) q2h and ensure total fluid intake <U/O by replacing every 1 cc U/O with 0.5 cc 1/2 NS IV (PO fluids if physiologic POD)
- avoid glucose-containing fluid replacement (can cause iatrogenic diuresis)
- check Na and K q6-12h and replace prn
- follow creatinine and BUN to baseline

Infectious and Inflammatory Diseases

Urinary Tract Infections (UTI)

- for UTIs during pregnancy, see *Obstetrics*, OB18

Definition

- greater than 100,000 bacteria/ml – midstream urine
 - if symptomatic, 100 bacteria/ml may be significant

Classification

- **uncomplicated:** lower urinary tract infection in a setting of functionally and structurally normal urinary tract
- **complicated:** pyelonephritis and/or structural/functional abnormality
- unresolved bacteriuria = urinary tract is not sterilized during therapy (most commonly due to resistant organisms or noncompliance)
- recurrent UTI
 - bacterial persistence = urine cultures become sterile during therapy but resultant reinfection of the urine by the same organisms
 - reinfection = new infection with new pathogen (80% of recurrent UTIs)

Source

- ascending (most common) – GI organisms
- hematogenous (TB, perinephric abscess)
- lymphatic
- direct (inflammatory bowel disease, diverticulitis)

Risk Factors

- stasis and obstruction:
 - residual urine in poorly flushing system, e.g. posterior urethral valves, reflux, medication (anticholinergics), BPH, urethral stricture, cystocele
- foreign body:
 - introduce pathogen or act as nidus of infection
 - e.g. catheter, instrumentation
- decreased resistance to organisms:
 - diabetes, malignancy, immunosuppression
- other factors:
 - trauma, anatomic variance (congenital), female (short urethra)

Clinical Features

- storage symptoms (frequency, urgency, dysuria)
- voiding symptoms (hesitancy, post-void dribbling, dysuria)
- hematuria
- pyelonephritis: more severe symptoms (including constitutional symptoms, CVA tenderness)

Organisms

- routine cultures (see sidebar)
- non-routine cultures:
 - tuberculosis (TB)
 - *Chlamydia trachomatis*
 - *Mycoplasma (Ureaplasma urealyticum)*
 - fungi (*Candida*)



**Cystitis: Common Pathogens
KEEPS**
Klebsiella sp.
E. coli (90%), other Gram-negatives
 Enterococci
Proteus mirabilis, *Pseudomonas*
S. saprophyticus, *S. fecalis*

Indications for Investigations

- persistence of pyuria/symptoms after adequate therapy
- severe infection with an increase in creatinine
- recurrent/persistent infections
- atypical pathogens (urea splitting organisms)

Investigations

- midstream urine R&M, C&S
 - dipstick: leukocytes \pm nitrites \pm hematuria
 - microscopy: >5 WBC/HPF in un-spun urine or >10 WBC/HPF in spun urine, bacteria, \pm WBC casts
 - Gram stain: GN bacilli, GP cocci, >1 bacterium/oil immersion field
 - culture and sensitivity: midstream, catheterized or suprapubic aspirate
- hematuria workup – urine cytology, ultrasound, cystoscopy
- CT scan if indicated

Treatment

- confirm diagnosis
- identify organism and treat (TMP/SMX, fluoroquinolones, nitrofurantoin, cephalosporins)
 - for mild infections 3 day course is sufficient (for treatment details see *Common Medications*, U43)
- establish predisposing cause (if any) and correct
- if febrile, consider admission with IV therapy and rule out obstruction

Recurrent/Chronic Cystitis

- incidence of bacteriuria in females:
 - pre-teens: 1%; late teens: 4%; 30-50 years: 6%
- assess predisposing factors as described above
- possible relation to intercourse (postcoital antibiotics), perineal colonization
- investigations may include cystoscopy, ultrasound, CT
- antibiotic prophylaxis if >3 or 4 episodes per year in females

Etiology

- unknown:
 - theories: increased epithelial permeability, autoimmune, neurogenic
 - associations: severe allergies, irritable bowel syndrome (IBS), fibromyalgia

Treatment

- daily low-dose prophylaxis (nitrofurantoin, TMP/SMX)
- lifestyle changes (limit caffeine intake, increase fluid/water intake, smoking cessation)
- post-menopausal women: consider topical or systemic estrogen therapy
- no treatment for asymptomatic UTI except in pregnant women or patients undergoing urinary tract instrumentation

Interstitial Cystitis (Painful Bladder Syndrome)

Definition

- chronic urgency, frequency \pm pain without other reasonable causation

Etiology

- unknown:
 - theories: increased epithelial permeability, autoimmune, neurogenic, defective glycosaminoglycan (GAG) layer overlying mucosa
 - associations: severe allergies, irritable bowel syndrome (IBS), fibromyalgia

Epidemiology

- prevalence: $\sim 20/100,000$
- 90% of cases are in females
- mean age at onset is 40 years

Classification

- non-ulcerative (more common) – younger to middle-aged
- ulcerative – middle-aged to older

Diagnosis

- required criteria:
 - glomerulations (submucosal petechiae) or Hunner's ulcers on cystoscopic examination
 - pain associated with the bladder or urinary urgency
 - negative urinalysis, C&S

Differential Diagnosis

- UTI, vaginitis, bladder tumour
- radiation/chemical cystitis
- eosinophilic/TB cystitis
- bladder calculi

Treatment

- patient empowerment (diet, lifestyle)
- pentosan polysulfate (Elmiron®)
- low dose amitriptyline
- bladder hydrodistention (also diagnostic) under general anesthesia
- intravesical dimethylsulfoxide (DMSO) or Cystistat®
- surgery (augmentation cystoplasty and urinary diversion ± cystectomy)

Acute Pyelonephritis

- see [Infectious Diseases](#), ID21

Definition

- infection of the renal parenchyma with local and systemic manifestations

Etiology

- ascending (usually GN bacilli) or hematogenous route (usually GP cocci)
- causative microorganisms: *E. coli* (most common), *Klebsiella*, *Proteus*, *Pseudomonas*, *Enterococcus faecalis*, *Enterobacter*, *S. Aureus*, *S. saprophyticus*
- common underlying causes of pyelonephritis: stones, strictures, prostatic obstruction, vesicoureteric reflux, neurogenic bladder, catheters, DM, sickle-cell disease, PCKD, immunosuppression, post-renal transplant, instrumentation, pregnancy

Clinical Features

- rapid onset (hours – day)
- LUTS including frequency, urgency, hematuria
- fever, chills, nausea, vomiting, myalgia, malaise
- CVA tenderness or exquisite flank pain
- dysuria is not a symptom of pyelonephritis without concurrent cystitis

Investigations

- urine R&M, C&S (see *Urinary Tract Infections*, U10)
- blood
 - CBC + differential: leukocytosis, left shift
- imaging – indicated if suspect complicated pyelonephritis or symptoms do not improve with 72 hours of treatment
 - Abdo/pelvic U/S
 - IVP
 - Cystoscopy
 - CT

Treatment

- may treat as outpatient if hemodynamically stable, ciprofloxacin PO x 7-14 days or cotrimoxazole (TMP/SMX) PO x 14 days
- severe or non-resolving: admit, hydrate and treat with ampicillin IV and gentamycin IV
- emphysematous pyelonephritis: emergency nephrectomy
- stone obstruction: admit and emergency stenting or percutaneous nephrostomy tube



MacroBID has poor tissue penetration and therefore is not used to treat pyelonephritis (requires post-renal uroconcentration).

Prostatitis/Prostatodynia

- most common urologic diagnosis in men <50 years
- incidence 10-30%
- acute bacterial, chronic bacterial, abacterial subtypes



Prostatic massage may cause extreme tenderness and increased risk of inducing sepsis, abscess or epididymo-orchitis.

Table 6. Comparison of the Three Types of Prostatitis

	Type I: Acute Bacterial Prostatitis	Type II: Chronic Bacterial Prostatitis	Type III: Chronic Pelvic Pain Syndrome (Abacterial)
Etiology	KEEPS (see U10 sidebar): 80% <i>E. coli</i> Ascending urethral infection and reflux into prostatic ducts Often associated with outlet obstruction (BPH), recent cystoscopy, prostatic biopsy Most infections occur in the peripheral zone (see Figure 6)	Recurrent exacerbations of acute prostatitis signs and symptoms Recurrent UTI with same organism	Divided into inflammatory and non-inflammatory subtypes Intraprostatic reflux of urine \pm urethral hypertonia Multifactorial (immunological, neuropathic, neuroendocrine, psychosocial)
Clinical Features	Acute onset fever, chills, malaise Rectal, lower back and perineal pain Storage and voiding LUTS Hematuria	Frequently asymptomatic with normal prostate on DRE	Pelvic pain, storage LUTS, ejaculatory pain, post-ejaculatory pain
Investigations	Rectal exam Enlarged, tender, warm prostate Urine C&S: 4 specimens VB1 (voided bladder urine): initial (urethra) VB2: midstream (bladder) EPS (expressed prostatic secretions): (prostate) not usually performed VB3: post-massage/DRE (prostate) Urine R&M Blood CBC, C&S	Urine C&S: 4 specimens Colony counts in EPS and VB3 should exceed those of initial and midstream by 10 times (suggests prostate as bacterial source)	DRE variable Urine C&S negative on serial specimens Prostate biopsy (rarely performed) shows histological inflammation
Treatment	Supportive measures (antipyretics, analgesics, stool softeners) PO antibiotics (Cipro [®] , Septra [®]) treat for 4-6 wks to prevent complications Admission criteria: sepsis, urinary retention, immunodeficiency IV antibiotics (ampicillin and gentamicin) if severe Mid-stream urine C&S at 1 and 3 months post antibiotic therapy Avoid catheterization due to risk of bacteremia and systemic infection Small drainage catheter may be inserted if obstruction suspected	Extended course of antibiotics (3-4 months) Fluoroquinolones, TMP/SMX or doxycycline; addition of an α -blocker may reduce symptoms	Trial of antibiotic therapy fluoroquinolone or doxycycline if <i>Chlamydia trachomatis</i> is suspected α -blocker to relieve sphincter spasms, NSAIDs and supportive measures for symptomatic relief

Epididymitis and Orchitis



Etiology

- infection:
 - <35 years – gonorrhea or *Chlamydia trachomatis*
 - >35 years + penetrative anal intercourse – GI organisms (esp. *E. coli*)
- mumps infection may involve orchitis after parotiditis
- other rare causes:
 - TB
 - syphilis
 - granulomatous (autoimmune) in elderly men
 - amiodarone (non-infectious cause, involves only head of epididymis)
- note: epididymitis is much more common than orchitis



If unsure between diagnoses of epididymitis and torsion: go to OR.
Remember: torsion > 6 hrs has poor prognosis.

Risk Factors

- UTI, unprotected sexual contact
- instrumentation/catheter
- reflux
- increased pressure in prostatic urethra (straining, voiding, heavy lifting) may cause reflux of urine along vas deferens \rightarrow sterile epididymitis



Prehn's sign: pain may be relieved with elevation of testicles in epididymitis but not in testicular torsion. Poor sensitivity, especially in children.

Clinical Features

- sudden onset scrotal pain and swelling \pm radiation along cord to flank
- scrotal erythema and tenderness
- fever
- storage symptoms, purulent discharge
- reactive hydrocele

Investigations

- urinalysis (pyuria), urine C&S
- \pm urethral discharge: Gram stain/culture
- if diagnosis uncertain, must do:
 - colour-flow Doppler ultrasound
 - nuclear medicine scan
 - examination under anesthesia

Treatment

- **rule out torsion**
- antibiotics:
 - *N. gonorrhoeae* or *C. trachomatis* – cefixime 400 mg PO once followed by azithromycin 1 g single dose or doxycycline 100 mg bid x 10 days
 - coliforms – broad spectrum antibiotics (Septra®, Cipro®) x 14 days
- scrotal support, ice, analgesia

Complications

- if severe \rightarrow testicular atrophy
- 30% have persistent infertility problems

Urethritis

- common causes: infectious, inflammatory (e.g. reactive arthritis)

Table 7. Infectious Urethritis: Gonococcal vs. Non-Gonococcal

	Gonococcal	Non-gonococcal
Causative organism	<i>Neisseria gonorrhoeae</i>	Usually <i>Chlamydia trachomatis</i>
Diagnosis	History of sexual contact, yellow purulent discharge, irritative LUTS Gram stain (GN diplococci), urine PCR and/or culture from urethral specimen	History of sexual contact, mucoid whitish purulent discharge, \pm irritative LUTS Gram stain demonstrates >4 PMN/oil immersion field, no evidence of <i>N. gonorrhoeae</i> , urine PCR and/or culture from urethral specimen
Treatment	Cefixime 400 mg PO once or Ceftriaxone 125 mg IM once AND treat for <i>Chlamydia trachomatis</i>	Azithromycin 1 g PO once or doxycycline 100 mg PO bid x 7 days



Reactive Arthritis (formerly known as Reiter's Syndrome)
Urethritis, Uveitis and Arthritis
(can't pee, can't see, can't climb a tree)

Urethral Syndrome

- dysuria in females with consistently sterile urine cultures or low bacterial counts
- some have bacterial urethrocystitis (*C. trachomatis* or other organisms) and require antimicrobial treatment
- treat: tetracycline or erythromycin
- rule out: vaginitis, cancer, interstitial cystitis, psychological etiologies

Stone Disease



Incidence

- prevalence of 2-3%
- male:female = 3:1, peak incidence 30-50 years of age
- recurrence rate: 10% at one year, 50% at 5 years, 60-80% lifetime

Clinical Features

- urinary obstruction → upstream distention → pain
 - flank pain from renal capsular distention (non-colicky)
 - severe waxing and waning pain radiating from flank to groin, testis, or tip of penis due to stretching of collecting system or ureter (ureteral colic)
- writhing, never comfortable, nausea, vomiting, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency)
- bladder stones result in: storage and voiding LUTS, terminal hematuria, suprapubic pain
- If fever, rule out concurrent pyelonephritis or obstruction

Differential Diagnosis of Renal Colic

- acute ureteral obstruction (other causes):
 - UPJ obstruction
 - sloughed papillae
 - clot colic from gross hematuria
- acute abdominal crisis – biliary, bowel, pancreas, abdominal aortic aneurysm (AAA)
- gynecological – ectopic pregnancy, torsion/rupture of ovarian cyst, pelvic inflammatory disease (PID)
- pyelonephritis (fever, chills, pyuria)
- radiculitis (L1) – herpes zoster, nerve root compression



Location of Stones

- calyx
 - may cause flank discomfort, recurrent infection or persistent hematuria
 - may remain asymptomatic for years and not require treatment
- pelvis
 - tend to cause obstruction at ureteropelvic junction (UPJ)
 - staghorn calculi (renal pelvis and one or more calyces)
 - often associated with infection that will not resolve until stone is cleared
- ureter
 - <5 mm diameter will pass spontaneously in 75% of patients



The four narrowest passage points for upper tract stones are:

1. UPJ
2. Pelvic brim
3. Under vas deferens/broad ligament
4. UVJ

Stone Pathogenesis

- supersaturation of stone constituents (at appropriate temperature and pH)
- stasis, low flow and low volume of urine (dehydration)
- crystal formation and stone nidus
- loss of inhibitory factors:
 - citrate (forms soluble complex with calcium)
 - magnesium (forms soluble complex with oxalate)
 - pyrophosphate
 - Tamm-Horsfall glycoprotein

Risk Factors

- hereditary: RTA, G6PD, cystinuria, xanthinuria, oxaluria, etc.
- dietary excess: Vitamin C, oxalate, purines, calcium
- dehydration (especially in summer months)
- sedentary lifestyle
- medications: thiazide
- UTI (with urea-splitting organisms)
- myeloproliferative disorders
- GI disorders: IBD
- hypercalcemia disorders: hyperparathyroidism, sarcoidosis, histoplasmosis, etc.

Approach to Renal Stone

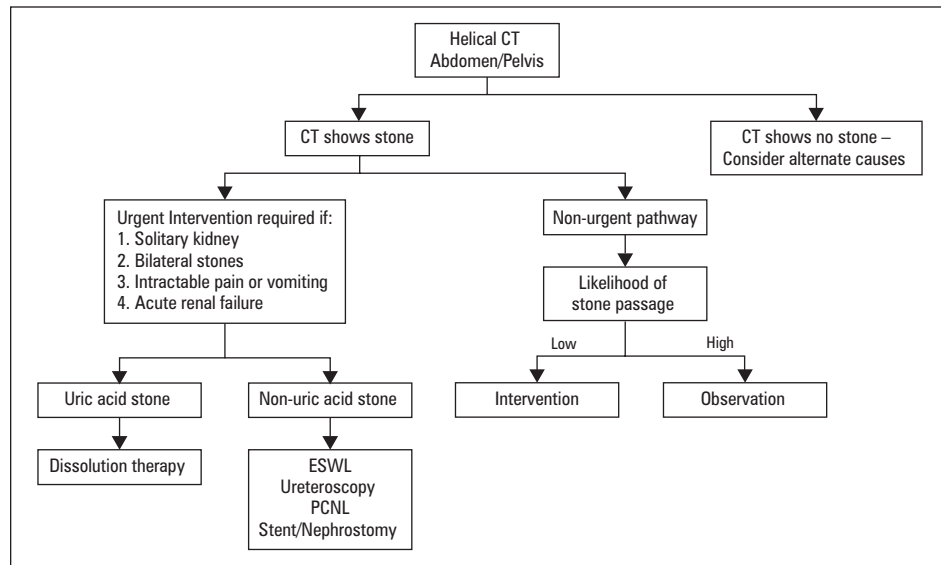


Figure 7. Approach to Renal Stone

Investigations

- screening labs
 - CBC → elevated WBC in presence of fever suggests infection
 - electrolytes, Cr, BUN → to assess renal function
 - urinalysis: R&M (WBCs, RBCs, crystals), C&S
- imaging
 - kidneys, ureters, bladders (KUB) x-ray
 - ♦ to differentiate opaque from non-opaque stones (e.g. uric acid, indinavir)
 - ♦ 90% of stones are radiopaque
 - CT scan
 - ♦ no contrast; good to distinguish radiolucent stone from soft tissue filling defect
 - abdominal ultrasound
 - ♦ may demonstrate stone (difficult in ureter)
 - ♦ may demonstrate hydronephrosis
 - IVP (not usually done)
 - ♦ anatomy of urine collecting system, degree of obstruction, extravasation
- cystoscopy for suspected bladder stone
- strain all urine → stone analysis
- if recurrent stone formers, conduct metabolic studies
 - serum electrolytes, Ca, PO₄, uric acid, creatinine and urea
 - PTH if hypercalcemic
 - 24 hour urine x 2 for creatinine, Ca, PO₄, uric acid, Mg, oxalate, citrate



	Radiopaque	Radiolucent
KUB	Calcium Struvite Cystine	Uric Acid Indinavir
CT	Calcium Struvite Cystine Uric Acid	Indinavir



Indications for admission to hospital:

1. Intractable pain
2. Intractable vomiting
3. Fever (suggests infection)
4. Compromised renal function
5. Single kidney with ureteral obstruction/bilateral obstructing stones



Stones and Infection

If septic, urgent ureteric stent or percutaneous nephrostomy should be considered.



Indications for Percutaneous Nephrolithotomy

- Size > 2.5 cm
- Staghorn
- UPJ obstruction
- Calyceal diverticulum
- Cystine stones (poorly fragmented with ESWL)

Treatment – Acute

- **medical**
 - analgesic (Tylenol #3®, Percocet®, Demerol®, morphine) ± antiemetic
 - NSAIDs help lower intra-ureteral pressure (e.g. Ketorolac)
 - alpha-blockers: increase rate of spontaneous passage in distal ureteral stones
 - ± antibiotics for UTI
 - IV fluids if vomiting (note: IV fluids do NOT promote stone passage)
- **interventional**: if obstruction endangers patient (i.e. sepsis, renal failure)
 - ureteric stent (via cystoscopy)
 - percutaneous nephrostomy (image-guided)
- **admit if necessary** – see sidebar

Treatment – Elective

- **medical**
 - conservative if stone < 5 mm and no complications
 - fluids to increase urine volume to > 2 L/day (3-4 L if cystine)
 - specific to stone type (Table 8)

- **interventional**

- kidney
 - ♦ stent if stone is 1.5-2.5 cm
 - ♦ extracorporeal shockwave lithotripsy (ESWL) if stone <2.5 cm
 - ♦ percutaneous nephrolithotomy if stone >2.5 cm (see sidebar U16)
- ureter
 - ♦ ESWL is the primary modality of treatment
 - ♦ ureteroscopy (extraction or fragmentation) if
 - failed ESWL
 - ureteric stricture
 - reasonable alternative for distal 1/3 of ureter
 - open ureterolithotomy (very rare)
- bladder
 - ♦ transurethral cystolitholapaxy
 - ♦ remove outflow obstruction (TURP or stricture dilatation)

- **Prevention**

- dietary modification:
 - increase fluid (>2 L/day), potassium intake
 - reduce animal protein, oxalate, sodium, sucrose, and fructose intake
 - avoid high-dose vitamin C supplements
- medications:
 - thiazide diuretics for hypercalciuria
 - allopurinol for hyperuricosuria
 - potassium citrate for hypocitraturia

Efficacy of α -Blockers for the Treatment of Ureteral Stones
J. Urol 2007; 1779:983-987

Study: Meta-analysis of prospective randomized trials comparing α -blockers to conservative therapy.
Data Sources: MEDLINE (January 1966 to October 2005), the Cochrane Central Search library, EMBASE (1980 to 2005), and the electronic database of abstracts presented at the Annual Meeting of the American Urological Association (2002 to 2005) were searched for literature published in English.

Patients: 11 studies met selection criteria (n=911). Treatment ranged from 8 days to 6 weeks.

Main Outcome: Incidence of distal ureteral stone expulsion.

Results: Administration of an α -blocker with conservative treatment increased incidence of stone expulsion over conservative treatment alone by 44% (95% CI 1.31-1.59, p<0.001).

Conclusion: α -blocker therapy is associated with significantly increased rates of distal ureteral stone expulsion.



Although hypercalciuria is a risk factor for stone formation, decreasing dietary calcium is NOT recommended to prevent stone formation. Low dietary calcium leads to increased oxalate absorption and higher urine levels of calcium oxalate.

Table 8. Stone Classification

Type of Stone	Calcium (75-85%)	Uric Acid (5-10%)	Struvite (5-10%)	Cystine (1%)
Etiology	Hypercalciuria Hyperuricosuria (25% of patients with Ca stones) Hyperoxaluria (<5% of patients) Hypocitraturia (12% of patients) Other causes: • Hypomagnesemia – associated with hyperoxaluria and hypocitraturia • High dietary sodium • Decreased urinary proteins	Uric acid precipitates in low volume, acidic urine with a high uric acid concentration: • Hyperuricosuria alone • Low urinary pH, low urine volume (e.g. GI water loss) • Drugs (ASA, thiazides) • Diet (purine rich red meats) • Hyperuricosuria with hyperuricemia • Gout • High rate of cell turnover or cell death (leukemia, cytotoxic drugs)	Infection with urea-splitting organisms (<i>Proteus</i> , <i>Pseudomonas</i> , <i>Providencia</i> , <i>Klebsiella</i> , <i>Mycoplasma</i> , <i>Serratia</i> , <i>S. aureus</i>) results in alkaline urinary pH and precipitation of struvite (magnesium ammonium phosphate)	Autosomal recessive defect in small bowel mucosal absorption and renal tubular absorption of dibasic amino acids results in "COLA" in urine (cystine, ornithine, lysine, arginine)
Key Features	Radiopaque on KUB Reducing dietary calcium is NOT an effective method of prevention/treatment	Radiolucent on KUB Radiopaque on CT Acidic urine	Perpetuates UTI because stone itself harbours organism Stone and all foreign bodies must be cleared to avoid recurrence Associated with staghorn calculi Positive urine dip and cultures Note: <i>E. coli</i> infection does not cause struvite stones	Aggressive stone disease seen in children and young adults Recurrent stone formation, family history Often staghorn calculi Faintly radiopaque on KUB Positive urine sodium nitroprusside test, urine chromatography for cystine
Treatment	Fluids to increase urine volume to >2 L/day <i>Medical if stone <5 mm and no complications</i> For calcium stones: cellulose phosphate, orthophosphate for absorptive causes <i>Procedural/Surgical treatment if stone >5 mm or presence of complications (see U16)</i> For calcium oxalate stones: thiazides, \pm potassium citrate, \pm allopurinol Calcium struvite – antibiotics (stone must be removed to treat infection)	Increased fluid intake Alkalinization of urine to pH 6.5 to 7 (bicarbonate, potassium citrate) \pm allopurinol Shockwave lithotripsy not effective	Complete stone clearance Antibiotics for 6 weeks Regular follow up urine cultures	Increased fluid intake (3-4L of urine/day) Alkalinize urine (bicarbonate, potassium citrate), Penicillamine/ α -MPG or Captopril (form complex with cystine) Shockwave lithotripsy not effective

Urological Neoplasms

Approach to Renal Mass

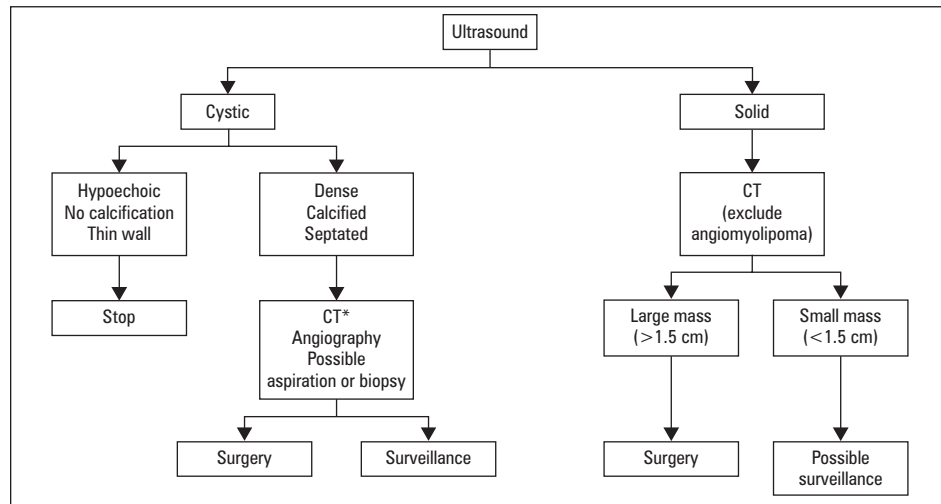


Figure 8. Workup of a Renal Mass

*MRI occasionally performed if contrast contraindicated

Benign Renal Neoplasms

RENAL CYSTS

- simple cysts
 - very common – up to 50% at age 50
 - usually incidental finding on abdominal imaging
- classification of cysts (i.e. simple and complex)
 - Bosniak classification is used to stratify for risk of malignancy based on cyst features, see Table 9
- polycystic kidney disease
 - autosomal recessive – massive kidneys with early renal failure in children
 - ♦ associated with hepatic disease
 - autosomal dominant – progressive bilateral disease leading to hypertension and renal failure
 - ♦ associated with hepatic cysts and cerebral aneurysms
- medullary sponge kidney
 - dilatations of the collecting ducts
 - usually benign course, but predispose to calcium phosphate stones
- von Hippel-Lindau syndrome
 - renal cysts, cerebellar and retinal hemangioblastomas, pancreatic and epididymal cysts
 - 30-40% incidence of renal cell carcinoma

Table 9. Bosniak Classification of Renal Cysts

Class	Description	Features	Risk of Malignancy
1	Simple cyst	Round, no septations, no calcifications, no solid component	Near zero
2	Minimally complex cyst	Thin septation, calcifications, hyperdense on CT	Minimal
3	Complex cyst	Thicker septations, thicker and more irregular walls, measurable enhancement	Moderate, surgical intervention usually necessary
4	Clearly malignant	Class 3 plus enhancing soft-tissue components	Near certain



Tuberous Sclerosis

Autosomal dominant syndrome characterized by mental retardation, epilepsy, adenoma sebaceum and other hamartomas.



Causes of Enlarged Kidneys

SHAPE

Scleroderma
HIV nephropathy
Amyloidosis
Polycystic kidney disease
Endocrinopathy (diabetes)

Table 10. Benign Renal Masses

	Angiomyolipoma (Renal Hamartoma)	Renal Oncocytoma	Renal Adenoma
Epidemiology	Less than 1% of adult renal tumours F > M 20% associated with tuberous sclerosis (especially if multiple, recurrent)	3-7% of renal tumours. More common in males	Incidence increases with age Found in 7-23% of all autopsies M:F = 3:1
Characteristics	Clonal neoplasm consisting of fat, smooth muscle and blood vessels May extend into renal vein and become symptomatic	Spherical, capsulated with possible central scar Histologically organized aggregates of eosinophilic cells originating from intercalated cells of collecting duct	Small cortical lesions <1 cm Majority are solitary but can be multifocal Histologically organized cells with no atypia which may exhibit trisomy of chromosomes 7 and 17
Diagnosis	Incidental diagnosis Negative attenuation (-20 HU) on CT is pathognomonic Rare presentation of hematuria, flank pain and palpable mass (same as RCC)	Incidental finding on CT although difficult to distinguish from RCC Biopsy may be performed to rule out malignancy	Incidental finding on CT Rarely symptomatic Controversy as to whether this represents benign or pre-malignant neoplasm
Management	Benign course although excision warranted if increased risk of rupture and retroperitoneal bleed (large size, pregnancy, previous bleed) Follow with serial U/S	Partial/radical nephrectomy for large masses High intensity focused ultrasound (HIFU) or radiofrequency ablation (RFA) for smaller masses	Partial/radical nephrectomy if mass >3cm due to increased risk of metastasis

Malignant Renal Neoplasms



RENAL ADENOCARCINOMA [Renal Cell Carcinoma (RCC)]

Etiology

- cause unknown
- originates from proximal convoluted tubule epithelial cells
- risk factors: smoking (results in 2x increased relative risk), cadmium exposure, employment in leather industry
- familial incidence seen with von Hippel-Lindau syndrome

Epidemiology

- eighth most common malignancy (accounts for 3% of all newly diagnosed cancers)
- 85% of primary malignant tumours in kidney
- male:female = 3:1
- peak incidence at 50-60 years of age

Pathology

- histological subtypes: clear, granular, spindle cell, papillary, chromophobe

Clinical Features

- usually asymptomatic – frequently diagnosed incidentally by U/S or CT
- poor prognostic indicators: weight loss, weakness, anemia, bone pain
- local effects: classic “too late triad” found in 10-15%:
 - gross hematuria 50%
 - flank pain <50%
 - palpable mass <30%
- was called the “internist’s tumour” because of paraneoplastic symptomatology, now called the “radiologist’s tumour” because of incidental diagnosis imaging
- systemic effects: paraneoplastic syndromes (10-40% of patients)
 - hematopoietic disturbances: anemia, polycythemia, raised ESR
 - endocrinopathies: hypercalcemia (increased vitamin D hydroxylation), erythrocytosis (increased erythropoietin), hypertension (increased renin), production of other hormones (prolactin, gonadotropins, TSH, insulin and cortisol)
 - hepatic cell dysfunction – “Stauffer’s syndrome”: abnormal liver function tests, decreased WBC count, fever, areas of hepatic necrosis; no evidence of metastases; reversible following removal of primary tumour
 - hemodynamic alterations: systolic hypertension (due to AV shunting), peripheral edema (due to caval obstruction)
- metastases: seen in 15% of new cases
 - bone, brain, lung and liver most common sites



Tumour may invade renal veins and inferior vena cava lumen (may result in ascites, hepatic dysfunction, right atrial tumour, and pulmonary emboli).

Investigations

- routine labs for paraneoplastic syndromes (CBC, ESR, LFTs)
- urinalysis (60-75% have hematuria)
- renal ultrasound (solid vs. cystic lesion)
- CT scan (to distinguish solid vs. cystic lesion and to determine extent and operability)
- IVP (mass lesion): no longer routinely done
- angiography: no longer routinely done

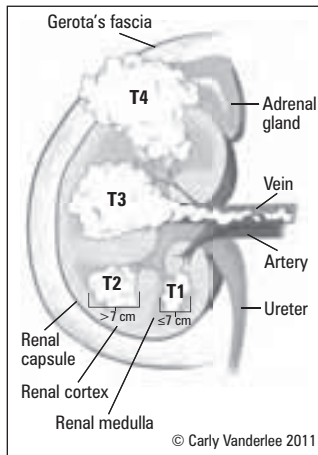


Figure 9. RCC Staging

Bevacizumab Plus Interferon Alfa Compared with Interferon Alfa Monotherapy in Patients with Metastatic Renal Cell Cancer: CALGB 90206. *Journal of Clinical Oncology* 2008; 26:5422-5428

Purpose: To investigate the role of anti-VEGF therapy in metastatic renal cell carcinoma (RCC) in combination with the standard first line treatment of interferon alpha (IFN).

Methods/Population: Patients with untreated metastatic RCC were randomized to receive either bevacizumab plus IFN or IFN alone (same dose). The primary end-point was overall survival, with progression-free survival (PFS) and safety measured as secondary end-points.

Results: 732 patients were enrolled between 2003 and 2005. 363 patients were randomly assigned to IFN monotherapy and 369 were randomly assigned to combination therapy. Median survival was improved in the group receiving combination therapy vs. monotherapy (8.5 months vs. 5.2 months, $p < 0.0001$). Toxicity was greater in the combination therapy group, significantly so for grade 3 hypertension (9% vs. 0%), anorexia (17% vs. 8%), fatigue (35% vs. 28%) and proteinuria (13% vs. 0%). No significant benefit in terms of overall survival was observed at the time of study closing.

Conclusions: The addition of bevacizumab to IFN therapy for the treatment of metastatic renal cell carcinoma provided significantly improved progression-free survival, but also demonstrated increased toxicity.



RCC Management

Surgery is the only effective intervention for RCC; chemotherapy is NOT useful.



Differential Diagnosis of Filling Defect

- Urothelial cell carcinoma (differentiate via cytology and CT scan)
- Uric acid stone (differentiate via cytology and CT scan)
- Blood clot
- Pyelitis cystica
- Papillary necrosis
- Fungus ball
- Gas bubble from gas producing organisms

Methods of Spread

- direct, venous, lymphatic

Staging

- involves CT, chest x-ray, liver enzymes and functions, bone scan

Table 11. TNM Classification of Renal Adenocarcinoma

T	N	M
T1: tumour < 7 cm, confined to renal parenchyma T1a: < 4 cm T1b: 4-7 cm	N0: no regional nodes N1: metastasis to a single node, < 2 cm	M0: no evidence of metastasis M1: presence of distant metastasis
T2: tumour > 7 cm, confined to renal parenchyma	N2: metastasis to a single node between 2 and 5 cm or multiple nodes < 2 cm	
T3: tumour extends into major veins or adrenal, but not beyond Gerota's fascia T3a: into adrenal or sinus fat T3b: into renal vein or infradiaphragmatic IVC T3c: into supradiaphragmatic IVC	N3: node > 5 cm	
T4: tumour extends beyond Gerota's fascia		

Treatment

- surgical:
 - radical nephrectomy: en bloc removal of kidney, tumour, ipsilateral adrenal gland (in upper pole tumours) and intact Gerota's capsule and paraaortic lymphadenectomy
 - partial nephrectomy: < 4 cm tumour or solitary kidney/bilateral tumours
 - surgical removal of solitary metastasis may be considered
- radiation for palliation – painful bony lesions
- chemotherapy: NOT effective
- advanced stage:
 - anti-angiogenesis (anti-VEGF)
 - anti-tyrosine kinase: sunitinib (Sutent®)
 - anti-IL2: daclizumab (Zenapax®)

Prognosis

- stage at diagnosis is the most important predictor of survival:
 - T1 – 5-year survival is 90-100%
 - T2-T3 – 5-year survival is approximately 60%
 - 5-year survival of patients presenting with metastasis is 0-20%

Carcinoma of the Renal Pelvis and Ureter

Epidemiology

- rare, accounts for 4% of all urothelial cancers
- frequently multifocal, 2-5% are bilateral
- M:F = 3:1
- relative incidence – bladder:renal:ureter = 100:10:1

Pathology

- papillary urothelial cell carcinoma (UCC); 85% (others include squamous cell, adenocarcinoma)
- UCC of kidney and ureter are histologically similar to bladder UCC

Risk Factors

- smoking
- chemical exposure (industrial dyes and solvents)
- analgesic abuse (acetaminophen, ASA, and phenacetin)
- Balkan nephropathy (chronic interstitial nephropathy in countries such as Serbia, Montenegro, Romania, Bulgaria)

Clinical Features

- gross painless hematuria (70-90% of patients)
- microscopic hematuria
- flank pain
- dysuria
- flank mass caused by tumour or associated hydronephrosis (10-20% of patients)

Investigations

- cystoscopy and retrograde pyelogram; CT scan, radiolucent filling defect on IVP/CT urogram

Treatment

- radical ureteronephrectomy with cuff of bladder
- distal ureterectomy for distal ureteral tumours

Bladder Carcinoma



Etiology

- unknown, but exposure to environmental and occupational carcinogens plays a role
- risk factors:
 - smoking (main factor – implicated in 60% of new cases)
 - chemicals: naphthylamines, benzidine, tryptophan, phenacetin metabolites
 - cyclophosphamide
 - prior history of radiation treatment to the pelvis
 - Schistosoma hematobium* infection (associated with SCC)
 - chronic irritation: cystitis, chronic catheterization, bladder stones, (associated with SCC)

Epidemiology

- 2nd most common urological malignancy
- male:female = 3:1, white:black = 4:1
- mean age at diagnosis is 65 years

Pathology

- classification:
 - urothelial cell carcinoma (UCC) >90%
 - squamous cell carcinoma (SCC) 5-7%
 - adenocarcinoma 1%
 - others <1%
- stages of urothelial cell carcinoma at diagnosis:
 - superficial papillary (75%) → >80% overall survival
 - 15% of these will progress to invasive UCC
 - the majority of these patients will have recurrence
 - invasive (25%) → 50-60% 5-year survival
 - 85% have no prior history of superficial UCC (i.e. *de novo*)
 - 15% have occult metastases at diagnosis – lymph nodes, lung, peritoneum, liver
- carcinoma in situ → flat, non-papillary erythematous lesion characterized by dysplasia confined to urothelium
 - more aggressive, poorer prognosis
 - usually multifocal
 - may progress to invasive UCC



The “field defect” theory helps to explain why UCC has multiple lesions and has a high recurrence rate. The entire urothelium (pelvis to bladder) is bathed in carcinogens.

Clinical Features

- hematuria (key symptom: 85-90% at the time of diagnosis)
- pain (50%)
- clot retention (17%)
- asymptomatic (20%)
- storage urinary symptoms – consider carcinoma in situ
- palpable mass on bimanual exam → likely muscle invasion
- obstruction of ureters → hydronephrosis and uremia (nausea, vomiting and diarrhea)
- metastases
 - hepatomegaly, lymphadenopathy, bone lesions
 - lower extremity lymphedema if local advancement or lymphatic spread

Investigations

- urinalysis, urine C&S, urine cytology
- ultrasound
- CT scan with contrast or intravenous pyelogram (IVP) → look for filling defect
- cystoscopy with bladder washings (gold standard)
- biopsy to establish diagnosis and to determine depth of penetration (although cold punch biopsy can be transurethral, resection is standard)
- new advances with specific bladder tumour markers (e.g. NMP-22, BTA, Immunocyt, FDP)

Grading

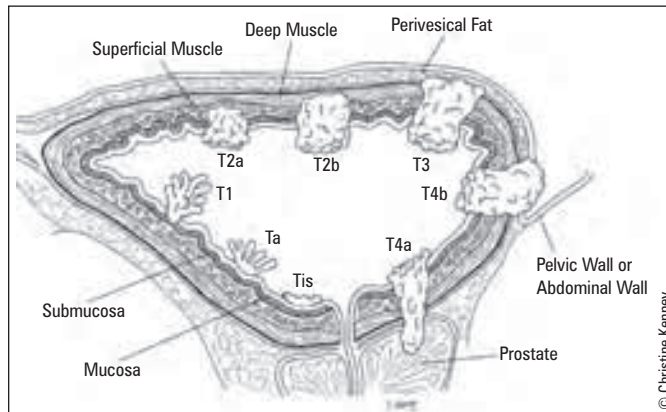
- Grade 1: well-differentiated (10% invasive)
- Grade 2: moderately differentiated (50% invasive)
- Grade 3: poorly differentiated (80% invasive)

Staging

- for invasive disease: CT or MRI, chest x-ray, liver function tests (metastatic work-up)

Table 12. TNM Classification of Bladder Carcinoma (Figure 10)

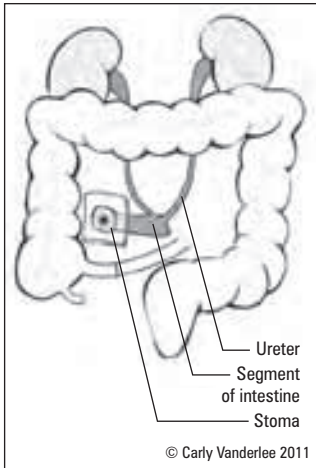
T	N	M
Ta: noninvasive papillary carcinoma	N status: as for renal cell carcinoma	M status: as for renal cell carcinoma
Tis: carcinoma in situ (CIS); flat tumour		
T1: tumour invades submucosa/lamina propria		
T2a: tumour invades superficial muscle		
T2b: tumour invades deep muscle		
T3: tumour invades perivesical fat		
T4a: adjacent organ involvement; prostate, uterus or vagina		
T4b: adjacent organ involvement; pelvic wall or abdominal wall		

**Figure 10. Urothelial Cell Carcinoma of Bladder****Treatment**

- superficial (non muscle invasive) disease: Tis, Ta, T1
 - transurethral resection of bladder tumour (TURBT) ± single dose or maintenance intravesical chemo/immuno-therapy (e.g. BCG, mitomycin C) to decrease recurrence rate
 - high grade disease – TURBT + maintenance BCG OR cystectomy in select patients
- invasive disease: T2a, T2b, T3
 - radical cystectomy + pelvic lymphadenectomy with urinary diversion (e.g. ileoconduit Figure 11) or irradiation for small tumours
- advanced/metastatic disease: T4a, T4b, N+, M+
 - initial combination systemic chemotherapy ± irradiation ± surgery

Prognosis

- depends on stage, grade, size, number of lesions, recurrence and presence of CIS:
 - stage T1 – 90% at 5 years
 - stage T2 – 55%
 - stage T3 – 20%
 - stage T4/N+/M+ – <5%

**Figure 11. Ileoconduit****Prostatic Carcinoma (CaP)****Etiology**

- not known
- risk factors
 - increased incidence in persons of African descent
 - family history
 - ♦ 1st degree relative = 2x risk
 - ♦ 1st and 2nd degree relatives = 9x risk
 - high dietary fat increases risk by 2x
 - cigarette smoking

Epidemiology

- most prevalent cancer in males
- third leading cause of male cancer deaths (following lung and colon)
- lifetime risk of a 50 y.o. man for CaP is 50%, and risk of death from CaP is 3%
- 75% diagnosed between ages of 60 and 85 and mean age at diagnosis is 72

Pathology

- adenocarcinoma
 - >95%
 - often multifocal
- urothelial cell carcinoma (4.5%)
 - associated with UCC of bladder
 - not hormone-responsive
- endometrial (rare)
 - carcinoma of the utricle

Anatomy (see Figure 6)

- 60-70% of nodules arise in the peripheral zone
- 10-20% arise in the transition zone
- 5-10% arise in the central zone

Clinical Features

- usually asymptomatic
- most commonly detected by DRE, elevated PSA, or as an incidental finding on transurethral resection of the prostate (TURP)
 - DRE: hard irregular nodule or diffuse dense induration involving one or both lobes
 - PSA: see *Prostate Specific Antigen*, U24
- locally advanced disease:
 - storage and voiding LUTS (uncommon without spread)
 - suspect with LUTS, incontinence ± back pain
- metastatic disease:
 - bony metastasis to axial skeleton is very common (osteoblastic)
 - visceral metastasis is less common with liver, lung and adrenal metastases occurring most frequently
 - leg pain and edema with nodal metastasis obstructing lymphatic and venous drainage

Methods of Spread

- local invasion
- lymphatic spread to regional nodes
 - obturator > iliac > presacral/para-aortic
- haematogenous dissemination occurs early

Investigations

- DRE
- PSA elevated in the majority of patients with CaP
- transrectal ultrasound (TRUS) → size and local staging
- TRUS-guided needle biopsy
- bone scan may be omitted in untreated CaP with PSA <10 ng/ml
- CT scanning to assess metastases

Table 13. Staging of Prostate Cancer (TNM 2002)

T	N	M
T1: clinically undetectable tumour, normal DRE and TRUS T1a: tumour incidental histologic finding in <5% of tissue resected T1b: tumour incidental histologic finding in >5% of tissue resected T1c: tumour identified by needle biopsy (because of elevated PSA level); tumours found in 1 or both lobes by needle biopsy but not palpable or reliably visible by imaging T2: palpable, confined to prostate T2a: tumour involving less than half a lobe T2b: tumour involving less than or equal to 1 lobe T2c: tumour involving both lobes T3: tumour extends through prostate capsule T3a: extracapsular extension (unilateral or bilateral) T3b: tumour invading seminal vesicle(s) T4: tumour invades adjacent structures (besides seminal vesicles)	N: spread to regional lymph nodes	M: distant metastasis M1a: nonregional lymph nodes M1b: bone(s) M1c: other site(s) with or without bone disease

Table 14. Prostate Cancer Mortality Risk

	Low Risk	Moderate Risk (if any of following)	High Risk (if any of following)
PSA	<10	10-20	>20
Gleason Score	<7	7	8-10
Stage	pT1-2a	pT2b-T2c	pT3/4

**Differential Diagnosis of a Prostatic Nodule**

- Prostate cancer (30%)
- Benign prostatic hyperplasia
- Prostatitis
- Prostatic infarct
- Prostatic calculus
- Tuberculous prostatitis

Effect of Selenium and Vitamin E on Risk of Prostate Cancer and other Cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

Lippman SM, Klein EA et al. *JAMA* 2009; 301(1):39-51

Methods: Randomized, placebo controlled trial with 35,533 men receiving selenium, vitamin E, selenium + vitamin E, or placebo.

Conclusion: Selenium or vitamin E, alone or in combination at the doses and formulations used, did not prevent prostate cancer in this population of relatively healthy men.

The Prostate Cancer Prevention Trial (PCPT)

NEJM 2003; 349:215-224

Study: A randomized, double-blind, placebo-controlled study designed to determine whether treatment with finasteride could reduce the prevalence of prostate CA during a 7-year period.

Patients: 18,882 men with elevated risk of prostate CA (55 years of age or older, African-American, or a 1st degree relative having prostate CA) with a normal DRE and a PSA level of ≤3 ng/mL were enrolled. 92% white.

Intervention: Finasteride (5 mg/day) vs. placebo
Main outcome: Prevalence of prostate CA during a 7-year period.

Results: Study was closed early as objectives were met. There was a 25% relative reduction ($P < 0.001$) in prevalence of prostate CA in the finasteride group [18% incidence] compared to placebo group [24% incidence], but an increase in the proportion of high-grade tumours (Gleason score 8-10) among those diagnosed with cancer (12% for finasteride, 5% for placebo). The majority of tumours in both groups (98%) were clinically localized disease (T1 or T2). The finasteride group also had a significantly higher incidence of sexual side effects, but fewer urinary symptoms than the placebo group.

Conclusions: Men over 55 who took finasteride for 7 years were 25% less likely to develop prostate CA compared to the placebo group, however the cancers in the finasteride group were of a higher grade.

**Considerations in Interpreting Prostate Biopsy Results**

- Gleason scores for two most predominant patterns are reported (e.g. 3+4 = Gleason sum)
 Note: 4+2 not equal to 3+4 despite equivalent Gleason sum
- Bilateral vs. uni-lobular involvement
- % of core and number of cores involved

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

NEJM 2005; 352:1977-84.

Purpose: To determine whether early radical prostatectomy improved the survival in men with non-invasive prostate cancer as compared to watchful waiting.

Methods/Population: 695 men were prospectively enrolled from 14 centres around Sweden, Finland and Iceland between 1989 and 1999. Inclusion criteria included being under the age of 75, newly diagnosed (and untreated) non-invasive prostate cancer, stage T2 or less. Pathology had to show either a moderately or well-differentiated tumour. Patients were randomly assigned one a 1:1 basis to either an intervention group (radical prostatectomy) or control (watchful waiting). The primary endpoint of the study was overall mortality due to prostate cancer, with secondary endpoints taken to be local progression and distant metastases. Analysis was performed on an intention-to-treat basis.

Results: The median follow-up was 8.2 years. The relative risk (RR) of local progression and distant metastases for the intervention group was 0.33 ($p < 0.001$) and 0.60 ($p < 0.01$) respectively, as compared to the control group. The relative risk of death due to prostate cancer in the intervention group was 0.56 ($p = 0.01$) as compared to controls.

Conclusions: Radical prostatectomy reduces the risk of death due to prostate cancer in men with non-invasive, well to moderately differentiated tumours, as compared to watchful waiting. The relative risk of both local invasion and the spread of distant metastases were also significantly decreased with early radical prostatectomy.

Treatment

- T1 (small well-differentiated CaP are associated with slow growth rate)
 - if young consider radical prostatectomy, brachytherapy or radiation
 - follow in older population (cancer death rate up to 10%)
- T2
 - radical prostatectomy or radiation (70-85% survival at 10 years) or brachytherapy
- T3, T4
 - staging lymphadenectomy and radiation or hormonal treatment
- N > 0 or M > 0 (see *Common Medications*, U43)
 - requires hormonal therapy/palliative radiotherapy for metastases
 - bilateral orchiectomy – removes 90% of testosterone
 - GnRH agonists [e.g. leuprolide (Lupron® or Eligard®), goserelin (Zoladex®)]
 - estrogens [e.g. diethylstilbestrol (DES)]
 - antiandrogens [bicalutamide (Casodex®)]
 - local irradiation of painful secondaries or half-body irradiation
 - chemotherapy regimens that include docetaxel may improve survival in advanced prostate cancer that is no longer responsive to hormone therapy

Table 15. Treatment Options for Localized Prostate Cancer

Modality	Population Considered	Limitations
Watchful Waiting (Active Surveillance)	Low grade disease or short life expectancy (<5-10 y); good follow-up	Disease progression
Brachytherapy	Low volume, low PSA (<10), low grade	Erectile dysfunction (50%), ? long term effectiveness
External Beam Therapy	Locally advanced disease, older patients	Radiation proctitis (5%), erectile dysfunction (50%), risk of rectal cancer
Radical Prostatectomy	Young patients (<65 y), high grade disease	Incontinence (10%), erectile dysfunction (30-50%)

* Other options include cryosurgery, high intensity focuses ultrasound (HIFU), hormonal ablation

Prognosis

- stage T1-T2: excellent, comparable with normal life expectancy
- stage T3-T4: 40-70% survival at 10 years
- stage N+ and/or M+: 40% survival at 5 years
- prognostic factors: tumour stage, tumour grade, PSA value, PSA doubling time

Prostate Specific Antigen (PSA)

- enzyme produced by epithelial cells of prostate gland to liquify the ejaculate
- leaks into circulation and is present at <4 ng/mL
- measured total serum PSA is a combination of free (unbound) PSA (15%) and complexed PSA (85%)

Screening Prostate Cancer: PSA and DRE

AUA Best Practice Statement, 2009 Update

- PSA may be elevated in prostate cancer and many other conditions; it is not specific to prostate cancer
- currently mixed evidence concerning effect of PSA screening on mortality (ERSPC and PLCO trials – see sidebar)
- population-based, routine screening not recommended
- must discuss risk factors, test characteristics, risk of over-detection and over-treatment, treatment and active surveillance options
- well-informed patients can elect to undergo PSA test and DRE
- the decision to proceed to prostate biopsy should be based primarily on PSA and DRE results, but should take into account multiple factors (free and total PSA, patient age, PSA velocity, PSA density, family history, ethnicity, prior biopsy history and comorbidities)

Strategies to Increase Specificity of PSA

- age-related cut-off values

Table 16. Normal PSA Value by Age Group

Age Range (years)	Serum PSA Concentration (µg/L)
40-49	<2.5
50-59	<3.5
60-69	<4.5
70-79	<6.5

Oesterling JE et al. JAMA 1993; 270(7):860-4.



PSA is specific to the PROSTATE, but NOT to prostate cancer.



In PSA testing, think “free and easy”: increased free/total ratio suggests benign cause of high PSA.



Causes of Increased PSA

BPH, prostatitis, prostatic ischemia/infarction, acute urinary retention, prostate biopsy/surgery, prostatic massage, urethral catheterization, TRUS, strenuous exercise, ejaculation, acute renal failure, coronary bypass graft, radiation therapy; a normal DRE does NOT significantly elevate PSA.

- free-to-total PSA ratio:
 - complexed PSA increases in prostate cancer, decreasing the percentage of the free fraction
 - <10% free PSA suggestive of cancer, >20% free suggests benign cause
- PSA velocity:
 - change of >0.75 ng/mL/year associated with increased risk of cancer
- PSA density:
 - PSA divided by prostate volume as found on TRUS
 - >0.15 ng/mL/g associated with increased risk of cancer

Other Uses for PSA (AUA Best Practice Statement, 2009 Update)

- therapeutic decision making: patients with serum PSA levels <10.0 ng/mL are most likely to respond to local therapy
- work-up: bone scans are generally not necessary in patients with newly diagnosed prostate cancer who have a PSA <20.0 ng/mL unless the history or clinical examination suggests bony involvement
- disease monitoring: serum PSA should fall to a low level following radiation therapy, high intensity focused ultrasound and cryotherapy and should not rise on successive occasions. PSA should remain undetectable following radical prostatectomy
- outcome prediction: in patients with metastatic disease receiving androgen suppression therapy, failure to achieve a PSA nadir of <4.0 ng/mL seven months after initiation of therapy is associated with a very poor prognosis (median survival: one year)

Testicular Tumours



Etiology (Risk Factors)

- cryptorchidism, atrophy, sex hormones, HIV infection, infertility
- family history, personal history of testis cancer

Epidemiology

- rare, but most common in young adults (17-37 years of age)
- high cure rate
- any solid testicular mass in young patient – must rule out malignancy
- slightly more common in right testis (corresponds with slightly higher incidence of right-sided cryptorchidism)
- 2-3% bilateral (simultaneously or successively)

Pathology

- primary:
 - 1% of all malignancies in males
 - most common solid malignancy in males aged 15-34 years
 - undescended testicle has increased risk (10-40x) of malignancy
 - 95% are germ cell tumours (all are malignant)
 - ♦ seminoma (35%) → classic, anaplastic, spermatocytic
 - ♦ nonseminomatous germ cell tumours (NSGCT) → embryonal cell carcinoma (20%), teratoma (5%), choriocarcinoma (<1%), yolk sac (<<1%), mixed cell type (40%)
 - 5% are non-germ cell tumours (usually benign) → Leydig (testosterone, precocious puberty), Sertoli (gynecomastia, decreased libido)
- secondary:
 - male >50 years of age
 - usually a lymphoma
 - metastases (e.g. lung, prostate, GI)

Clinical Features

- **painless** testicular enlargement (painful if intratesticular hemorrhage or infarction)
- firm, non-tender mass
- dull, heavy ache in lower abdomen, anal area or scrotum
- associated hydrocele in 10%
- coincidental trauma in 10%
- infertility (rarely presenting complaint)
- gynecomastia due to secretory tumour effects
- metastatic disease related back pain
- supraclavicular and inguinal nodes
- abdominal mass (retroperitoneal lymph node metastases)

Screening and Prostate-Cancer Mortality in a Randomized European Study

NEJM 2009; 360:1320-8

Purpose: To determine the efficacy of prostate-specific antigen (PSA) screening in improving overall survival in prostate cancer.

Method/Population: 182 160 patients aged 50-74 were recruited between 1994 - 2004 from multiple European countries and prospectively enrolled and randomized to either a screening or control group. Screening consisted of a PSA level taken every 4 years (if negative) and cut-off for biopsy was at 3ng/mL. Treatment of confirmed prostate cancer was left to the guidelines of each country. The primary end-point was overall mortality, analyzed on an intention-to-screen basis.

Results: Median follow-up time was 9 years, and the incidence of prostate cancer in the screening group was 8.2% vs. 4.8% in the control group. The relative risk of death in the screening group vs. control was 0.80 (p<0.05). The absolute risk reduction was 0.71 deaths per 1000 men in the screening group, translating to a number needed to screen of 1410 and a number needed to treat of 48.

Conclusions: The use of PSA screening was able to confer a relative risk reduction of 20% to men between the age of 50 and 74 (with the majority of benefit seen in men aged 50-69). However the increased rate of diagnosis was significantly increased in the screening group, and due to the indolent course of many prostate cancers, this fact must be taken into consideration. Further study is warranted to examine the optimal screening strategies in terms of PSA timing and thresholds to help formulate the optimal strategy to balance the risks of overdiagnosis and reduced prostate cancer mortality.



Orchiopexy

Surgical descent (orchiopexy) of undescended testis does not reduce the risk of malignancy. It can however, reduce the risk of infertility and facilitates physical exam.



Trauma is not a cause of tumour, but often prompts medical evaluation.



Testes and scrotum have different lymphatic drainage, therefore trans-scrotal approach for biopsy or orchiectomy should be avoided.



Aorta is on the Left: Left testicle drains into the pre and paraaortic nodes.
IVC is on the Right: Right testicle drains into the paracaval nodes.



Staging

Clinical – CXR (lung metastases), markers for staging (β-hCG, AFP, LDH), CT abdomen/pelvis (retroperitoneal lymphadenopathy)

- Stage I: disease limited to testis, epididymis or spermatic cord
- Stage II: disease limited to the retroperitoneal nodes
- Stage III: disease metastatic to supradiaphragmatic nodal or visceral sites

Pathologic (at orchiectomy)

- T1: tumour confined to testis and epididymis, no vascular/lymphatic invasion
- T2: tumour extends beyond tunica albuginea or vascular/lymphatic invasion
- T3: tumour involves spermatic cord
- T4: tumour invades scrotum
- T4a: tumour invades spermatic cord
- T4b: tumour invades scrotal wall



RPLND can be performed in a nerve sparing fashion, preserving nerves of the hypogastric plexus to maintain antegrade ejaculation.

Methods of Spread

- local spread follows lymphatics:
 - right → medial, paracaval, anterior and lateral nodes
 - left → left lateral and anterior paraaortic nodes
 - “cross-over” metastases from right to left are fairly common, but they have not been reported from left to right
- hematogenous most commonly to lung, liver, bones and kidney

Investigations

- diagnosis is established by radical inguinal orchiectomy
- tumour markers:
 - beta-hCG and AFP are positive in 85% of non-seminomatous tumours
 - pre-orchidectomy elevated marker levels return to normal post-operatively if no secondaries
 - beta-hCG positive in 7% of seminomas, AFP never elevated with seminoma
- testicular ultrasound (hypoechoic area within tunica albuginea = high suspicion of testicular cancer)
- evidence of testicular microlithiasis is not a risk factor for testicular cancer
- needle aspiration contraindicated

Management

- orchiectomy for all stages
- adjuvant therapies as per Figure 12

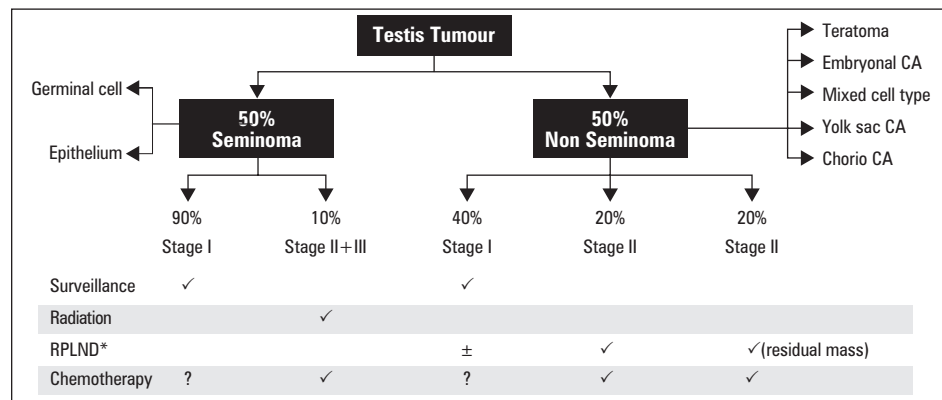


Figure 12. Management of Testicular Cancer

*RPLND = retroperitoneal lymph node dissection Adapted from Dr. MAS Jewett

Prognosis

- 99% cured with stage I, stage II disease
- 70-80% complete remission with advanced disease

Penile Tumours

- rare (<1% of cancer in males in U.S.), most common in 6th decade

Benign

- cyst, hemangioma, nevus, papilloma

Pre-malignant

- balanitis xerotica obliterans, leukoplakia, Buschke-Lowenstein tumour (large condyloma)

Pre-invasive Cancer

- carcinoma in situ (CIS):
 - Bowen's disease → crusted, red plaques on the shaft
 - erythroplasia of Queyrat → velvet red, ulcerated plaques on the glans
 - treatment options: local excision, laser, radiation, topical 5-fluorouracil

Malignant

- risk factors:
 - chronic inflammatory disease
 - STI
 - phimosis
 - uncircumcised penis
- 2% of all urogenital cancers
- squamous cell (>95%), basal cell, melanoma, Paget's disease of the penis (extremely rare)
- definitive diagnosis requires full thickness biopsy of lesion

Table 17. TNM Staging for Penile Carcinoma

T	N	M
Tx: primary tumour cannot be assessed	N1: metastasis in a single superficial, inguinal lymph node	M: presence (+) or absence (0) of distant metastasis (lung, liver, bone, brain)
T0: no evidence of primary tumour	N2: metastasis in multiple or bilateral superficial lymph nodes	
Tis: CIS	N3: metastasis in deep inguinal or pelvic lymph node(s) unilateral	
Ta: non-invasive carcinoma		
T1: tumour invades subepithelial connective tissue (Buck's and Dartos fascia)		
T2: tumour invades corpus spongiosum or cavernosum (through tunica albuginea)		
T3: tumour invades urethra or prostate		
T4: tumour invades other adjacent structures		

- lymphatic spread (superficial/deep inguinal nodes → iliac nodes) >> hematogenous

Treatment

- wide surgical excision with tumour-free margins (dependent on extent and area of penile involvement) ± lymphadenectomy

Scrotal Mass

- see *Common Presenting Problems*, U3

Table 18. Differentiating between Scrotal Masses

Condition	Pain	Palpation	Additional Findings
Torsion	+	Diffuse tenderness	Absent cremaster reflex, negative Prehn's sign, EMERGENCY!
Epididymitis	+	Epididymal tenderness	Present cremaster reflex, positive Prehn's sign
Orchitis	+	Diffuse tenderness	Present cremaster reflex, positive Prehn's sign
Hematocele	+	Diffuse tenderness	No transillumination
Hydrocele	–	Testis not separable from hydrocele, cord palpable	Transillumination
Spermatocele	–	Testis separable from spermatocele, cord palpable	Transillumination
Varicocele	–	Bag of worms	No transillumination
Indirect Inguinal	– (+ if strangulated)	Testis separable from hernia, cord not palpable, cough impulse may transmit, may be reducible	No transillumination
Tumour	– (+ if hemorrhagic)	Hard lump/nodule	
Idiopathic	–		

**Differential of a Benign Scrotal Mass****HIS BITS**

Hydrocele
 Infection (epididymitis/.Orchitis)
 Sperm (spermatocele)
 Blood (hematocele)
 Intestines (hernia)
 Torsion
 Some veins (varicocele)



Acute scrotal swelling/pain in young boys is torsion until proven otherwise.



In an isolated right-sided varicocele, beware of a right retroperitoneal mass.

**Varicocele Grading**

Grade 1: Palpable only with valsalva manoeuvre
 Grade 2: Palpable without valsalva
 Grade 3: Visible through scrotal skin

**Indications for Treatment of Varicocele**

- Impaired sperm quality or quantity
- Pain or dull ache affecting quality of life
- Affected testis fails to grow in adolescents
- Cosmetic indications (especially in adolescents)

Table 19. Benign Scrotal Masses

Type	Varicocele	Spermatocele	Hydrocele	Testicular Torsion	Inguinal Hernia
Definition	Dilatation and tortuosity of pampiniform plexus	A benign, sperm filled epididymal retention cyst	Collection of serous fluid that results from a defect or irritation in the tunica vaginalis	Twisting of the testicle causing venous occlusion and engorgement as well as arterial ischemia and infarction	Protrusion of abdominal contents through the inguinal canal into the scrotum
Etiology	<ul style="list-style-type: none"> • 10% of men • Due to incompetent valves in the testicular veins • 90% left sided 	Multiple theories, including: <ul style="list-style-type: none"> • Distal obstruction • Aneurysmal dilations of the epididymis • Agglutinated germ cells 	<ul style="list-style-type: none"> • Usually idiopathic • Found in 5-10% testicular tumours • Associated with trauma/infection • Communicating: patent processus vaginalis, changes size during day (peds) • Non-communicating: non-patent processus vaginalis (adult) 	<ul style="list-style-type: none"> • Trauma, • Cryptorchidism, • "Bell clapper deformity" • Many occur in sleep (50%) • Necrosis of glands in 5-6 hours 	<ul style="list-style-type: none"> • Indirect (through internal ring, often into scrotum) – congenital • Direct (through external ring, rarely into scrotum) – abdominal muscle weakness
History/Physical Exam	<ul style="list-style-type: none"> • "Bag of worms", • Often painless • Pulsates with valsalva 	<ul style="list-style-type: none"> • Non-tender, cystic mass • Transilluminates 	<ul style="list-style-type: none"> • Non-tender, intrascrotal mass • Cystic • Transilluminates 	<ul style="list-style-type: none"> • Acute onset severe scrotal pain, swelling • GI upsets cases • Retracted and transverse testicle (horizontal lie) • Negative Phren's sign • Absent cremasteric reflex 	<ul style="list-style-type: none"> • A small bulge in the groin that may increase in size and disappear when lying down • Can present as a swollen or enlarged scrotum • Discomfort or sharp pain – especially when straining, lifting, or exercising
Investigations	<ul style="list-style-type: none"> • Physical exam • Valsava 	<ul style="list-style-type: none"> • Physical exam • U/S to r/o tumour 	<ul style="list-style-type: none"> • U/S to r/o tumour 	<ul style="list-style-type: none"> • U/S with colour flow Doppler probe over testicular artery • Decrease uptake on 99m Tc-pertechnetate scintillation scan (doughnut sign) 	<ul style="list-style-type: none"> • History and physical • Invagination of the scrotum • Valsalva
Treatment	<ul style="list-style-type: none"> • Conservative • Surgical ligation of testicular veins • Percutaneous vein occlusion (balloon, sclerosing agents) • Repair may improve sperm count/motility 50-75%. 	<ul style="list-style-type: none"> • Conservative • Avoid needle aspiration as it can lead to infection, reaccumulation and spilling of irritating sperm within scrotum • Excise if symptomatic 	<ul style="list-style-type: none"> • Conservative • Needle drainage • Surgical 	<ul style="list-style-type: none"> • Emergency manual detorsion (rotate outward) with elective bilateral orchiopexy • Failure of manual detorsion: surgical detorsion with orchiopexy • Orchiectomy if poor prognosis 	<ul style="list-style-type: none"> • Surgical repair

TORSION OF TESTICULAR APPENDIX

- twisting of testicular/epididymal vestigial appendix
- often <16 years of age

Signs and Symptoms

- clinically similar to testicular torsion
- "blue dot sign" – blue infarcted appendage seen through scrotal skin (can usually be palpated as small, tender lump)
- point tenderness over the superior-posterior portion of testicle

Treatment

- analgesia – most will subside over 5-7 days
- surgical exploration and excision if diagnosis uncertain or refractory pain

HEMATOCELE

- trauma with bleed into tunica vaginalis
- ultrasound helpful to exclude fracture of testis which requires surgical repair

Treatment

- ice packs, analgesics, surgical repair

Penile Complaints

Peyronie's Disease

Definition

- benign curvature of penile shaft secondary to fibrous thickening of tunica albuginea
- commonly on dorsal surface resulting in upward curvature of erect penis – may occur at any site

Etiology

- exact etiology unknown
- trauma/repeated microtrauma → inflammation → fibrosis
- familial predisposition
- related to diabetes mellitus, vascular disease, autoimmunity, Dupuytren's contracture
- role of vitamin E deficiency, beta-blockade, elevated serotonin

Clinical Features

- penile curvature and/or pain with erection
- penile shortening and poor erection distal to plaque

Treatment

- depends on pain and interference with intercourse
- watchful waiting (spontaneous resolution in up to 50%)
- vitamin E, potassium paraaminobenzoate (potaba) – limited efficacy
- intralesional verapamil
- surgery if stable disease, significant deformity AND failed medical therapy
 - excision of plaque ± prosthesis

Priapism

UROLOGICAL EMERGENCY

Definition

- prolonged unwanted erection lasting >4 hours
- tumescence (swelling) of corpora cavernosa (often painful) with flaccid glans penis (no corpora spongiosum involvement)

Classification

- low-flow (most common): reduced/absent cavernosal blood flow → hypoxia, acidosis → ischemia
- high-flow: unregulated arterial flow with normal tissue oxygenation

Etiology

- primary – 60% idiopathic
- secondary:
 - thromboembolic – including sickle cell, thalassemia, total parenteral nutrition, dialysis, leukemia, solid tumours
 - neurogenic – spinal cord injury, autonomic neuropathy
 - traumatic – cavernosal artery laceration, arterio-venous fistula
 - medication – intracavernosal drug injection (e.g. triple mix), alpha-blockers, anticoagulants, antidepressants, antipsychotics, anxiolytics,
 - recreational drugs – cocaine, marijuana, alcohol

Treatment

- treat reversible causes (e.g. leukapheresis if leukemia, treat sickle cell crisis)
- high flow often self-limited – observation vs. arterial embolization
- low flow:
 - urgent decompression via needle aspiration of blood
 - phenylephrine injection into the corpora cavernosa q10-15min
 - shunt creation between cavernosum and spongiosum if no response within 1 hour

Complications

- erectile dysfunction due to corporal fibrosis if treatment delayed (50%)
 - 90% risk if >24 hours

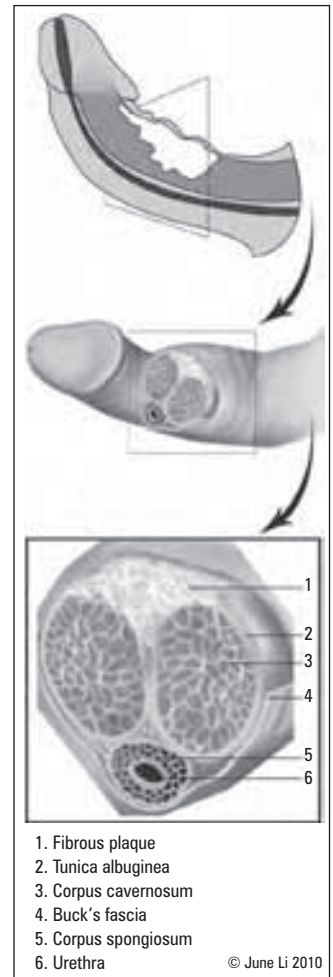


Figure 13. Peyronie's Disease

Paraphimosis

UROLOGICAL EMERGENCY

Definition

- foreskin caught behind glans leading to edema → unable to reduce foreskin

Treatment

- squeeze edema out of the glans with manual pressure (analgesia required)
- pull on foreskin with fingers while pushing on glans with thumbs
 - if fails, perform dorsal slit or circumcision
- elective circumcision for definitive treatment (paraphimosis tends to recur)

Complications

- infection, glans ischemia, gangrene

Phimosis

Definition

- inability to retract foreskin over glans penis
- may be caused by balanitis (infection of glans), often due to poor hygiene or congenital
- normal congenital adhesions separate naturally by 1-2 years of age

Treatment

- circumcision, dorsal slit, proper hygiene (trial of topical corticosteroids in children)

Complications

- balanoposthitis (inflammation of prepuce), paraphimosis, penile cancer



Erectile Dysfunction (ED)

Definition

- consistent (>3 months duration) or recurrent inability to obtain or maintain an adequate erection for sexual performance

Physiology

- erection involves the coordination of psychologic, neurologic, hemodynamic, mechanical and endocrine components
- nerves: sympathetic (T11-L2), parasympathetic (S2-4), somatic [dorsal penile/pudendal nerves (S2-4)]
- erection ("POINT")
 - parasympathetics → release of nitric oxide (NO) → increased cGMP levels within corpora cavernosa leading to:
 1. arteriolar dilatation
 2. sinusoidal smooth muscle relaxation → increased arterial inflow and compression of penile venous drainage (decreased venous outflow)
- emission ("SHOOT")
 - sensory afferents from glans
 - secretions from prostate, seminal vesicles, and ejaculatory ducts enter prostatic urethra (sympathetics)
- ejaculation ("SHOOT")
 - bladder neck closure (sympathetic)
 - spasmodic contraction of bulbo-cavernosus and pelvic floor musculature (somatic)
- detumescence
 - sympathetic nerves, norepinephrine, endothelin-1 → arteriolar and sinusoidal constriction → penile flaccidity



Erections POINT AND SHOOT
parasympathetics = **point**; and
sympathetics/somatics = **shoot**

Classification

Table 20. Classification of Erectile Dysfunction

	Psychogenic	Organic
Proportion	10%	90%
Onset	Sudden	Gradual
Frequency	Sporadic	All circumstances
Variation	With partner and circumstance	No
Age	Younger	Older
Organic Risk Factors (HTN, DM, Dyslipidemia)	No organic risk factors	Risk factors present
Nocturnal/AM erection	Present	Absent

Etiology ("IMPOTENCE")

- Iatrogenic: pelvic surgery/pelvic radiation
- Mechanical: Peyronie's, post-priapism
- Psychological: depression, stress, anxiety, PTSD, widower syndrome
- Occlusive vascular: arterial (hypertension, diabetes, smoking, hyperlipidemia, peripheral vascular disease, smoking), venous (impaired veno-occlusion)
- Trauma: penile/pelvic
- Extra factors: renal failure, cirrhosis, COPD, sleep apnea, malnutrition
- Neurogenic: CNS (e.g. Parkinson's, multiple sclerosis, spinal cord injury, Guillain-Barré, spina bifida, stroke), PNS (e.g. diabetes, peripheral neuropathy)
- Chemical: antihypertensives, sedatives, antidepressants, antipsychotics, anxiolytics, anti-androgens (including 5-alpha reductase inhibitors), statins, GnRH agonists, illicit drugs
- Endocrine: diabetes, hypogonadism, hyperprolactinemia, hypo/hyperthyroid

Diagnosis

- complete history (sexual, medical, and psychosocial)
- self-administered questionnaires (International Index of Erectile Function, Sexual Health Inventory for Men Questionnaire, ED Intensity Scale, ED Impact Scale)
- focused physical exam, including vascular and neurologic examinations
- lab investigations – based on clinical picture
 - risk factor evaluation: fasting blood glucose or HbA1c, cholesterol profile
 - other: TSH, CBC, urinalysis
 - hypothalamic-pituitary-gonadal axis evaluation: testosterone (free and total), prolactin, LH, FSH
- usually unnecessary to do further testing except in certain situations
- specialized testing
 - non-invasive:
 - ♦ nocturnal penile tumescence monitor
 - invasive (rarely done):
 - ♦ intracavernous injection of papaverine or PGE₁ – rule out significant arterial or venous impairment
 - ♦ Doppler studies pre- and post-papaverine injection – cavernosal anatomy and arterial flow evaluation (penile-brachial index <0.6 suggestive of vascular cause)
 - ♦ angiography of pudendal artery post papaverine injection – post-traumatic ED evaluation only for possible vascular reconstruction
 - ♦ dynamic cavernosometry and cavernosography – to evaluate leakage from penile veins



Testosterone deficiency is an uncommon cause of ED.

Treatment

- must fully inform patient/partner of options, benefits and complications
- non-invasive:
 - lifestyle changes (alcohol, smoking), psychological (sexual counseling and education)
 - change precipitating medications
- minimally invasive:
 - oral medication (see *Common Medications*, U43)
 - ♦ sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®): inhibits phosphodiesterase type 5
 - ♦ rarely used
 - yohimbine: α -blocker that is best for psychogenic ED
 - trazodone: serotonin antagonist and reuptake inhibitor
 - androgen replacement therapy: if hypogonadism
 - vacuum devices: draw blood into penis via negative pressure, then put ring at base of penis once erect
 - MUSE: Male Urethral Suppository for Erection – vasoactive substance (PGE₁) capsule into urethra
- invasive:
 - intracorporal vasodilator injection/self-injection
 - ♦ triple therapy (papaverine, phentolamine, PGE₁) or PGE₁ alone
 - ♦ complications include priapism (overdose), thickening of tunica albuginea at site of repeated injections (Peyronie's plaque) and hematoma
 - implants (last resort): malleable or inflatable
 - vascular surgery: microvascular arterial bypass and venous ligation (investigational)



PDE-5 inhibitors are contraindicated in patients on nitrates/nitroglycerin due to severe hypotension.

Premature Ejaculation

Definition

- occurrence of ejaculation prior to when one or both partners desire it
- primary premature ejaculation
 - never experienced sexual activity without the presence of premature ejaculation
- secondary premature ejaculation
 - the individual once had acceptable ejaculatory control, but now experiences premature ejaculation, not associated with a general medical condition

Epidemiology

- 30-70% prevalence
- most common sexual dysfunction reported in men 18-30 years old, associated with secondary impotence in men 45-65 years old

Investigations

- indicated by history and physical
- testosterone levels if in conjunction with impotence

Treatment

- must rule out and treat any associated general medical conditions (i.e. fear of angina)
- often thought to be due to psychological factors; identify and address specific stressors
- referral to psychiatry, couples counseling or sex therapy
- SSRIs have been found to be effective in some cases
- clomipramine (daily or PRN 4-6 hours before intercourse)

Trauma

- see [Emergency Medicine](#), ER14

Renal Trauma

Etiology

- blunt (80%, motor vehicle collision (MVC), assaults, falls) vs. penetrating (20%, stab wounds and gunshots)

History

- mechanism of injury

Physical Exam

- ABCs, renal vascular injury → shock mandating resuscitation
 - upper abdominal/flank tenderness, flank contusions, lower rib/vertebral transverse process fracture suggests blunt trauma

Investigations

- urinalysis: hematuria – requires workup but degree does not correlate with the severity of injury
- imaging: CT (contrast, triphasic) if patient stable – look for renal laceration, extravasation of contrast, retroperitoneal hematoma, and associated intra-abdominal organ injury

Staging

- I: contusion/hematoma
- II: <1 cm laceration without urinary extravasation
- III: >1 cm laceration without urinary extravasation
- IV: urinary extravasation
- V: shattered kidney or avulsion of pedicle

Classification According to Severity

- minor: contusions and superficial lacerations/hematomas – 90% of all blunt traumas, surgical exploration seldom necessary
- major: laceration that extends into medulla and collecting system, major renal vascular injury, shattered kidney

Management

- microscopic hematuria + isolated well-staged minor injuries → no hospitalization
- gross hematuria + contusion/minor lacerations → hospitalize, bedrest, repeat CT if bleeding persists

- surgical intervention:
 - absolute indications: hemorrhage and hemodynamic instability
 - relative indications
 - ♦ non-viable tissue and major laceration
 - ♦ urinary extravasation
 - ♦ vascular injury
 - ♦ expanding or pulsating peri-renal mass
 - ♦ laparotomy for associated injury

Outcome

- follow up with ultrasound or CT before discharge, and at 6 weeks
- hypertension in 5% of renal trauma

Bladder Trauma

- blunt (MVC, falls, and crush injury) vs. penetrating trauma to lower abdomen, pelvis, or perineum
- blunt trauma is associated with pelvic fracture in 97% of cases

Clinical Features

- abdominal tenderness, distention, and inability to void
- may be peritoneal signs or symptoms
- associated injuries including pelvic and long bone fractures are common
- hemodynamic instability due to extensive blood loss in the pelvis
- suprapubic discomfort and/or tenderness

Investigations

- urinalysis – gross hematuria in 90%
- imaging
- cystogram and post-drainage film for extravasation

Classification

- contusions: no urinary extravasation, damage to mucosa or muscularis
- intraperitoneal ruptures: often involve the bladder dome
- extraperitoneal ruptures: involve anterior or lateral bladder wall in full bladder

Treatment

- penetrating trauma: surgical exploration
- contusion: urethral catheter until hematuria completely resolves
- extraperitoneal bladder perforations: typically non-operative with Foley insertion
 - surgery if: infected urine, rectal/vaginal perforation, bony spike into bladder or if laparotomy for concurrent injury
- intraperitoneal rupture usually requires surgical repair and suprapubic catheterization

Complications

- complications of bladder injury itself are rare
- mortality is around 20%, and is usually due to associated injuries rather than bladder rupture

Urethral Injuries

Etiology

- posterior urethra: common site of injury is junction of membranous and prostatic urethra due to blunt trauma, MVCs, pelvic fracture
 - shearing force on fixed membranous and mobile prostatic urethra
- anterior urethra: straddle injury can crush bulbar urethra against pubic rami
- other causes: iatrogenic (instrumentation, prosthesis insertion), penile fracture, masturbation with urethral manipulation
- always look for associated bladder rupture

Clinical Features

- blood at urethral meatus
- high riding prostate on digital exam
- sensation of voiding without urine output
- swelling and butterfly perineal hematoma
- distended bladder
- penile and/or scrotal hematoma

Investigations

- do not perform cystoscopy or catheterization before retrograde urethrography if urethral trauma suspected
- retrograde urethrography – demonstrates extravasation and location of injury



All patients with suspected urethral injury should undergo retrograde urethrogram (RUG).



Do not catheterize if suspect urethral injury.

Treatment

- simple contusions – no treatment
- partial urethral disruption:
 - very gentle attempt at catheterization by urology staff or urology resident
 - with no resistance to catheterization – Foley x 2-3 weeks
 - with resistance to catheterization – suprapubic cystostomy or urethral catheter alignment in OR
- periodic flow rates/urethrograms to evaluate for stricture formation
- complete disruption:
 - immediate repair if patient stable, delayed repair if unstable (suprapubic tube in interim)



Infertility

Definition

- failure to conceive after one year of unprotected, properly timed intercourse
- incidence:
 - 15% of all couples – investigate both partners
 - 1/3 female, 1/3 male, 1/3 combined problem
 - primary (has never conceived before) vs. secondary (has conceived before)

Female Factors

- see Gynecology, GY21

Male Factors

Male Reproduction

- hypothalamic-pituitary-testicular axis (HPTA): GnRH from hypothalamus acts on anterior pituitary stimulating release of LH and FSH
 - LH acts on Leydig (interstitial) cells → testosterone synthesis/secretion
 - FSH acts on Sertoli cells → structural and metabolic support to developing spermatogenic cells
 - FSH and testosterone support germ cells (responsible for spermatogenesis)
- sperm route: epididymis → vas deferens → ejaculatory ducts → prostatic urethra

Etiology

- idiopathic (25% infertile males)
- endocrine (see Endocrinology, E48)
 - hypothalamic-pituitary-testicular axis (2-3%)
 - e.g. Kallmann's syndrome, excess prolactin, excess androgens, excess estrogens
- testicular
 - varicocele (35-40% infertile males)
 - tumour
 - congenital (Klinefelter's triad: small, firm testes, gynecomastia and azoospermia)
 - post-infectious (epididymo-orchitis, STIs, mumps)
 - uncorrected torsion
 - cryptorchidism (<5% of cases)
- obstructive
 - iatrogenic (vasectomy, hernia repair, hydrocelectomy, orchidopexy)
 - infectious (gonorrhea, chlamydia)
 - trauma
 - congenital (absence of vas deferens, cystic fibrosis)
 - bilateral ejaculatory duct obstruction, epididymal obstructions
 - Kartagener's syndrome
- retrograde ejaculation secondary to bladder/prostate surgery
- medications (chemotherapeutics, GnRH agonists, anabolic steroids)
- drugs (marijuana, cocaine, tobacco, alcohol)
- increased testicular temperature (sauna, hot baths, tight pants or underwear)
- chronic disease: liver, renal

History

- medical history (past illness, diabetes, trauma, CF, genetic syndromes)
- surgical history (orchidopexy, cryptorchidism, prostate)
- fertility history (pubertal onset, previous pregnancies, duration of infertility, treatments)
- sexual history (erection/ejaculation, timing, frequency, STIs)
- family history
- medications (e.g. nitrofurantoin, cimetidine, sulfasalazine, spironolactone, alpha-blockers)
- social history (alcohol, tobacco, cocaine, anabolic steroids)
- occupational exposures

Physical Exam

- general appearance (sexual development, gynecomastia)
- scrotal exam (size, consistency and nodularity of testicles; palpation of cord; DRE)

Investigations

- semen analysis (SA) at least 2 specimens over several weeks
- hormonal evaluation – indicated with abnormal semen analysis (rare to be abnormal with normal SA)
 - testosterone for evaluation of HPA
 - FSH measures state of sperm production
 - serum LH and prolactin are measured if testosterone or FSH are abnormal
- genetic evaluation
 - chromosomal studies (Klinefelter's Syndrome – XXY)
 - genetic studies (Y-chromosome microdeletion, CF gene mutation)
- immunologic studies (antisperm antibodies in ejaculate and blood)
- testicular biopsy
- scrotal U/S (varicocele, testicular size)
- vasography (assess patency of vas deferens)

Treatment

- lifestyle
 - regular exercise, healthy diet
 - eliminate lifestyle habits described above
- medical
 - endocrine therapy (see Endocrinology, E48)
 - treat retrograde ejaculation
 - discontinue anti-sympathomimetic agents, may start α -adrenergic stimulation (phenylpropanolamine, pseudoephedrine, or ephedrine)
 - treat underlying infections
- surgical
 - varicolectomy (if indicated)
 - vasovasostomy (vasectomy reversal)
 - epididymovasostomy
 - transurethral resection of blocked ejaculatory ducts
- assisted reproductive technologies (ART) – refer to infertility specialist
 - sperm washing + intrauterine insemination (IUI)
 - in vitro fertilization (IVF)
 - intracytoplasmic sperm injection (ICSI)



WHO Guidelines

Normal Semen Values

- Volume: 2-5 ml
- Concentration: > 20 million sperm/ml
- Morphology: 30% normal forms
- Motility: > 50% adequate forward progression
- Liquefaction: complete in 20 minutes
- pH: 7.2-7.8
- WBC: < 10 per high power field or < 10⁶ WBC/mL semen



Mutation of Cystic Fibrosis

Transmembrane Conductance Regulator (CFTR) gene associated with congenital bilateral absence of vas deferens (CBAVD) and epididymal cysts, even if patient manifests no symptoms of CF.



Common Terminology on Semenanalysis:

- Teratospermia: Abnormal morphology
- Asthenospermia: Abnormal motility
- Oligospermia: Decreased sperm count
- Azoospermia: Absent sperm in semen
- Mixed types, i.e. oligoasthenospermia

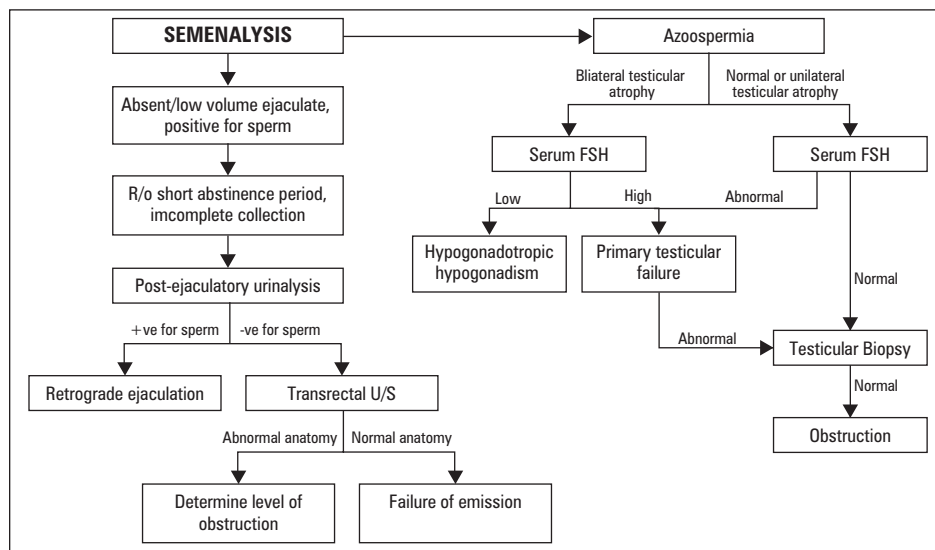


Figure 14. Infertility Workup

Pediatric Urology

Congenital Abnormalities

- not uncommon; 1/200 have congenital abnormalities of the GU tract
- UTI is the most common presentation postnatally
- hydronephrosis is the most common finding antenatally
- six common presentations of congenital urological abnormalities:



Majority of antenatal hydronephroses resolve during pregnancy or within the first year of life.

1. ANTENATAL HYDRONEPHROSIS

- 1 in 500 fetal U/S – detectable on U/S as early as first trimester
- most common urological consultation in perinatal period
- can be unilateral or bilateral
- important to examine the rest of the GU system for anomalies
- differential diagnosis
 - UPJ or UVJ obstruction
 - multi-cystic kidney
 - reflux
 - posterior urethral valves
 - duplication anomalies
- antenatal in utero intervention rarely indicated unless posterior urethral valves

2. POSTERIOR URETHRAL VALVES (PUV)

- the most common obstructive urethral lesion in male infants
- abnormal mucosal folds at the distal prostatic urethra causing varying degrees of obstruction
- most commonly recognized on prenatal ultrasound examination → bilateral hydronephrosis, thickened bladder, oligohydramnios

Clinical Presentation – depends on age and severity

- antenatal: bilateral hydronephrosis, distended bladder, oligohydramnios
- neonatal (recognized at birth): palpable abdominal mass (distended bladder, hydronephrosis), ascites (transudation of retroperitoneal urine), respiratory distress (pulmonary hypoplasia resulting from oligohydramnios) and features of oligohydramnios
- neonatal (not recognized at birth): within weeks present with urosepsis, dehydration, electrolyte abnormalities, failure to thrive
- toddlers: presents with urinary infections or voiding dysfunction
- school-aged boys: voiding dysfunction → urinary incontinence

Associated Findings

- oligohydramnios – due to low intrauterine production of urine
- renal dysplasia – due to high pressure reflux
- pulmonary hypoplasia secondary to oligohydramnios

Diagnosis

- VCUG → dilated and elongated posterior urethra, reflux

Treatment

- immediate catheterization to relieve obstruction, followed by cystoscopic resection of PUV

3. UPJ OBSTRUCTION

- the most common congenital defect of the ureter (but can be secondary to tumour, stone, etc.)
- M:F = 2:1
- 40% bilateral
- unclear etiology: adynamic segment of ureter, stenosis, strictures, aberrant blood vessels → extrinsic compression

Clinical Presentation

- symptoms depend on severity and age at diagnosis (mostly asymptomatic finding on antenatal U/S)
 - infants: abdominal mass, urinary infection
 - children: pain, vomiting, failure to thrive
 - some cases are diagnosed after puberty and into adulthood

Diagnosis

- antenatal U/S most common, Doppler U/S, IVP, and renal scan ± furosemide

Treatment

- surgical correction (pyeloplasty), consider nephrectomy if <15% renal function

Prognosis

- good since usually unilateral disease

4. VESICoureTERAL REFLUX (VUR)

- common condition wherein urine passes retrograde from the bladder through the UVJ into the ureter
- incidence ranges from 1-18.5% in normal children
- present in up to 70% of children with UTI
- 85% of VUR occurs in females but a male presenting with UTI has a higher likelihood of having VUR
- common cause of antenatal hydronephrosis
- 30-50% of children with reflux will have renal scarring
- common causes: trigonal weakness, lateral insertion of the ureters, short submucosal segment (all part of "primary reflux")
- many other causes including secondary reflux, infravesical obstruction, iatrogenic, secondary to ureteric abnormalities (e.g. ureterocele, ectopic ureter, or duplication), and secondary to cystitis

Presentation

- UTI, urosepsis
- pyelonephritis
- pain on voiding
- symptoms of renal failure (uremia, hypertension)
- diagnosis and staging is done using VCUG ± U/S

Complications

- pyelonephritis
- hydroureter/hydronephrosis

Treatment (see sidebar for grading)

- many children "outgrow" reflux (60% of primary reflux)
- annual renal U/S and VCUG/RNC to monitor; renal scan if suspect new renal scar (episode of pyelonephritis)
- treatment is dependent on the grade:
 - medical (grade I-III) – goal is to keep urine free of infection to prevent renal damage while waiting for child to "outgrow" their reflux
 - long term antibiotic prophylaxis at half the treatment dose for half the treatment time (TMP/SMX, amoxicillin, or nitrofurantoin)
 - surgical (ureteroneocystostomy ± ureteroplasty) or subureteral injection of Deflux® or Macroplastique®
 - ♦ indications:
 - failure of medical management
 - new renal scars
 - breakthrough infections
 - high grade reflux (grade IV or V – not an absolute indication)
- prognosis depends on degree of damage at the time of diagnosis

5. HYPOSPADIAS

- a condition in which the urethral meatus opens on the ventral side of the penis, proximal to the glans penis
- very common; 1/300 live male births
- multifactorial genetic mode of inheritance
- white >> black
- may be associated with chordee, intersex states, undescended testicles or inguinal hernia
- depending on the severity, there may be difficulty directing the urinary stream or infertility (long-term)
- treatment is surgical correction – optimal repair before 2 years old
- circumcision should be deferred because the foreskin may be utilized in the correction

**VUR Grading (based on cystogram)**

Grade I: ureters only fill

Grade II: ureters and pelvis fill

Grade III: ureters and pelvis fill with some dilatation

Grade IV: ureters, pelvis and calyces fill with significant dilatation

Grade V: ureters, pelvis and calyces fill with major dilatation and tortuosity

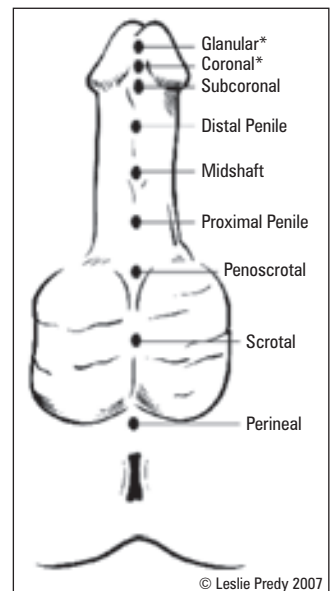


Figure 15. Classification of Hypospadias (*account for 75%)



Do not circumcise patients with hypospadias.

6. EPISPADIAS-EXSTROPHY COMPLEX

- rare: incidence 1/30,000, 3:1 male to female predominance
- epispadias-exstrophy complex: a spectrum of defects – depends on the timing of the rupture of the cloacal membrane
 - bladder exstrophy (congenital absence of a portion of lower abdominal and anterior vesical wall, with eversion of bladder)
 - ♦ several variants
 - cloacal exstrophy (vesicointestinal fissure)
 - ♦ most severe
 - ♦ exposed bladder, bowel and colon with imperforate anus
 - ♦ associated with spina bifida in >50%
 - epispadias
 - ♦ least severe
 - ♦ urethra opens on dorsal penis
- high morbidity → incontinence, infertility, reflux

Etiology

- represents failure of closure of the cloacal membrane, resulting in the bladder and urethra opening directly through the abdominal wall

Treatment

- surgical correction at birth, later corrections for incontinence, increasing bladder capacity and vesicoureteral reflux may be needed

Nephroblastoma (Wilm's Tumour)

- arises from abnormal proliferation of metanephric blastoma
- 5% of all childhood cancers, 5% bilateral
- average age of incidence is 3 years
- 1/3 hereditary (autosomal dominant) and 2/3 sporadic
 - familial form associated with other congenital abnormalities and gene defects

Clinical Features

- abdominal mass: large, firm, unilateral (most common presentation – 80%)
- hypertension (60%)
- flank tenderness
- microscopic hematuria
- nausea/vomiting

Treatment

- always investigate contralateral kidney
- treatment of choice is radical nephrectomy ± radiation ± chemotherapy

Prognosis

- generally good; overall 5-year survival about 80%
- metastatic disease may respond well

Cryptorchidism/Ectopic Testes

- definition: testes located abnormally somewhere along the normal path of descent (prepubic > external inguinal ring > inguinal canal > abdominal)
- ectopic testis (testis found outside its normal path of descent) is rare
- incidence:
 - 2.7% of full term newborns
 - 0.7%-0.8% at 1 year old
- differential diagnosis:
 - retractile testes
 - atrophic testes
 - intersex state (bilateral impalpable testes)

Treatment

- undescended testes should be brought down to monitor for malignancy and preserve fertility (better in less than 1 year of age)
- hormonal therapy (hCG or LH may facilitate their descent → not proven)
- surgical → orchiopexy



Normal Testicular Development and Descent in Utero

2nd Month – Testicle begins to form

4th Month – Begins to take on its normal appearance and migrates from its origin at the kidney to the internal inguinal ring

7th Month – The testis, surrounded in peritoneal covering, begins to descend through the internal ring, inguinal canal and external ring to terminate in the scrotum

Prognosis

- untreated bilateral cryptorchidism ~100% infertility
- treated bilateral: 60-70% fertility rate (dependent on the age at the time of surgery)
- treated/untreated unilateral: fertility is still less than the general population
- risk of malignancy is 10-40x increased in undescended testes; this risk does not decrease with surgical descent, but monitoring is made easier
- increased risk of testicular torsion (always perform bilateral orchiopexy for prevention if doing orchiopexy for torsion)

Disorders of Sexual Differentiation**Definition and Classification**

- genitalia that do not have a normal appearance based on the chromosomal sex of the child due to the undermasculinization of genetic males or the virilization of genetic females
- considered a social emergency
- four major categories
 1. 46 XY DSD
 - ♦ defect in testicular synthesis of androgens
 - ♦ androgen resistance in target tissues
 - ♦ palpable gonad
 2. 46 XX DSD
 - ♦ most due to congenital adrenal hyperplasia (21-hydroxylase deficiency most common enzymatic defect) → shunt in steroid biosynthetic pathway leading to excess androgens
 3. ovotesticular DSD
 4. mixed gonadal dysgenesis (46 XY/45 XO most common karyotype)
 - ♦ presence of Y chromosome → partial testis determination to varying degrees

Diagnosis and Treatment

- thorough maternal and family history needed
- other forms of abnormal sexual development:
 - maternal medication or drug use in pregnancy → maternal hyperandrogenemia
 - parental consanguinity
- physical exam: palpable gonad (= chromosomal male), hyperpigmentation, evidence of dehydration, hypertension, stretched phallus length, position of urethral meatus
- chromosomal evaluation – sex karyotype
- laboratory test:s:
 - plasma 17-OH-progesterone (after 36 hours of life) → increased in 21-hydroxylase deficiency (CAH)
 - plasma 11-deoxycortisol → increased in 11-β-hydroxylase deficiency
 - basal adrenal steroid levels
 - serum testosterone and DHT pre- and post-hCG stimulation (2,000 IU/day for 4 days)
 - serum electrolytes
- ultrasound of adrenals, gonads, uterus, and fallopian tubes
- endoscopy and genitography of urogenital sinus
- sex assignment (with extensive family consultation)
 - must consider capacity for sexually functioning genitalia in adulthood and psychologic impact
- reconstruction of external genitalia – between 6-12 months
- long term psychological guidance and support for both patient and family

Circumcision**Definition**

- removal of some or all of the foreskin from the penis

Epidemiology

- 30% worldwide
- frequency varies depending on geographic location, religious affiliation, socioeconomic classification

Medical Indications

- phimosis
- definitive treatment of paraphimosis

Contraindications

- unstable or sick infant
- congenital genital anomalies (hypospadias)
- family history of bleeding disorders warrants laboratory investigation prior to circumcision

Male Circumcision for Prevention of Heterosexual Acquisition of HIV in Men

Cochrane Database Syst Rev 2009; (2):CD003362

Background: This review evaluates the effectiveness and safety of male circumcision for preventing acquisition of HIV in heterosexual men. The analysed data is from three randomised controlled trials to assess the efficacy of male circumcision for preventing HIV acquisition in men in Africa which began in 2002.

Conclusions: This review found strong evidence that medical male circumcision reduces the acquisition of HIV by heterosexual men (between 38% and 66% over 24 months).

Circumcision Status and Risk of HIV and Sexually Transmitted Infections among Men who have Sex with Men: A Meta-analysis

JAMA 2008; 300(14):1674-84.

Background: This meta-analysis examined 15 studies (n= 53 567) that quantitatively examined the association between male circumcision and HIV/STI among men who have sex with men (MSM).

Results: The odds of being HIV-positive were not significantly lower among in circumcised MSM. The association between male circumcision and HIV was protective but not statistically significant. Male circumcision had a protective association with HIV in studies of MSM conducted before the introduction of highly active antiretroviral therapy.

Conclusions: This analysis found insufficient evidence that male circumcision protects against HIV infection or other STIs. However, the comparable protective effect of male circumcision in MSM studies conducted before the era of highly active antiretroviral therapy, supports further investigation of male circumcision for HIV prevention among MSM.

Complications

- bleeding
- infection
- phimosis, skin bridges
- fistula
- glans injury
- penile sensation deficits

Enuresis

- see [Pediatrics](#), P12

Selected Urological Procedures**Bladder Catheterization**
Steps to Maintaining Sterility in Bed Side Bladder Catheterization (NEJM Videos in Clinical Medicine Series)

1. Explain procedure to the patient and ensure no contraindications (blood at meatus, scrotal hematoma, pelvic fracture, high-riding prostate)
2. Ensure you have catheter and kit, lidocaine jelly and catheter tape within reach at the bedside
3. If patient is uncircumcised, don non-sterile gloves and retract foreskin
4. Insert 10-15ml of lidocaine jelly into urethral meatus and pinch tip of penis for a few minutes
5. Open kit and place between patient's legs
6. Don sterile gloves
7. Soak cotton balls in antiseptic
8. Open lubricant and dispel onto catheter tray
9. Attach syringe of water and collecting system to catheter
10. Place fenestrated drape over pubic region and proximal thighs
11. Grasp penile shaft with non-dominant hand, hold penis taut and perpendicular to the patient's body (this hand is now non-sterile)
12. Cleanse glans penis in circular motion
13. Lubricate tip of catheter, insert into urethral meatus and advance to the level of the balloon inflation port
14. Wait for return of urine into collecting system (apply suprapubic pressure if necessary)
15. Once urine is flowing, inflate balloon without allowing catheter to retract
16. Gently pull catheter back and tape to patient's thigh (tape the catheter, not the collecting system tubing)
17. Reduce foreskin to prevent paraphimosis

- catheter size measured by the French (Fr) scale – circumference in mm
- each 1 mm increase in diameter = approximately 3 Fr increase (standard size 16-18 Fr)

Continuous Catheterization

- indications:
 - accurate monitoring of urine output
 - relief of urinary retention due to medication, neurogenic bladder or intravesical obstruction
 - temporary therapy for urinary incontinence
 - perineal wounds
 - clot removal (24-28 Fr) for continuous bladder irrigation (CBI)
 - post-operative

Intermittent Catheterization

- indications:
 - post-void residual volume measurement
 - to obtain sterile diagnostic specimens for urinalysis/cultures
 - management of neurogenic bladder or chronic urinary retention

Causes of Difficult Catheterizations and Treatment

- patient discomfort – use sufficient lubrication (\pm xylocaine)
- collapsing catheter – lubrication as above \pm firmer catheter (silastic catheter)
- meatal/urethral stricture – dilate with progressively larger catheters/balloon catheter
- BPH – use coude catheter as angled tip can help navigate around prostate
- urethral disruption/obstruction – filiform catheter or suprapubic catheterization
- anxious patient – anxiolytic medication

Complications of Catheterization

- infection – UTI
- meatal/urethral trauma

Contraindications

- urethral trauma: blood at the meatus of the urethra, scrotal hematoma, pelvic fracture, and/or high riding prostate

Cystoscopy**Objective**

- endoscopic inspection of the lower urinary tract (urethra, prostate, bladder neck, walls and dome, and ureteral orifices) using irrigation, illumination, and optics
- scopes can be flexible or rigid

Indications

- hematuria
- LUTS (irritative or obstructive)
- urethral and bladder neck strictures
- stones
- bladder tumour surveillance
- evaluation of upper tracts with retrograde pyelography (ureteric stents, catheters)

Complications

- during procedure
 - infection, bleeding, anesthetic-related
 - perforation (rare)
- post-procedure (short-term)
 - epididymo-orchitis (rare)
 - urinary retention
- post-procedure (long-term)
 - stricture

Radical Prostatectomy

Objective

- the removal of the entire prostate and prostatic capsule via a lower midline abdominal incision, laparoscopically or robotically
 - internal iliac and obturator vessel lymph nodes may also be dissected and sent for pathology (dependent on risk: clinical stage, grade, PSA)
 - seminal vesicle vessels are also ligated

Indications

- treatment for localized prostate cancer

Complications

- immediate (intraoperative)
 - blood loss
 - rectal injury
 - ureteral injury (extremely rare)
- perioperative
 - lymphocele formation
- late
 - moderate to severe urinary incontinence (3-10%)
 - mild urinary incontinence (20%)
 - erectile dysfunction (~50%, depending on whether one, both, or neither of the neurovascular bundles are involved in extracapsular extension of tumour)

Transurethral Resection of the Prostate (TURP)

Objective

- to partially resect the periurethral area of the prostate (transition zone) to decrease symptoms of urinary tract obstruction
- accomplished via a cystoscopic approach using an electrocautery loop, irrigation (glycine), and illumination

Indications

- obstructive uropathy (large bladder diverticula, renal insufficiency)
- refractory urinary retention
- recurrent UTIs
- recurrent gross hematuria
- bladder stones
- intolerance/failure of medical therapy

Complications

- acute:
 - intra- or extraperitoneal rupture of the bladder
 - rectal perforation
 - incontinence
 - incision of the ureteral orifice (with subsequent reflux or ureteral stricture)
 - hemorrhage
 - epididymitis
 - sepsis
 - transurethral resection syndrome (also called “post-TURP syndrome”)
 - ♦ caused by absorption of a large volume of the hypotonic irrigation solution used, usually through perforated venous sinusoids, leading to a hypervolemic hyponatremic state
 - ♦ characterized by dilutional hyponatremia, confusion, nausea, vomiting, hypertension, bradycardia, visual disturbances, CHF, and pulmonary edema
 - ♦ treat with diuresis and (if severe) hypertonic saline administration

- chronic:
 - retrograde ejaculation (>75%)
 - erectile dysfunction (5-10% risk increases with increasing use of cautery)
 - incontinence (<1%)
 - urethral stricture
 - bladder neck contracture

Extracorporeal Shock Wave Lithotripsy (ESWL)

Objective

- to treat renal calculi, proximal calculi, and midureteral calculi which cannot pass through the urinary tract naturally
- shockwaves are generated and focused onto stone → fragmentation, allowing stone fragments to pass spontaneously and less painfully

Indications

- potential first-line therapy for renal and ureteral calculi less than 2.5 cm in size
- individuals with calculi in solitary kidney
- individuals with hypertension, diabetes or renal insufficiency

Contraindications

- acute urinary tract infection or urosepsis
- bleeding disorder or coagulopathy
- pregnancy
- obstruction distal to stone

Complications

- bacteriuria
- bacteremia
- post-procedure hematuria
- ureteric obstruction (by stone fragments)
- peri-nephric hematoma

Common Medications

Table 21. Antibiotics

Drug	Indications	Duration of Treatment	Limitations to Use
TMP/SMX	Simple uncomplicated cystitis Recurrent cystitis Pyelonephritis Prostatitis Epididymitis/orchitis (Gram-negative organism)	3 days Long term as prophylaxis 14 days 4-6 weeks 2 weeks	Stevens-Johnson syndrome ?Safety in last 2 weeks of pregnancy Resistance = 20% in the community
nitrofurantoin	Simple uncomplicated cystitis Recurrent cystitis	7 days	Contraindicated in renal failure Pulmonary toxicity/fibrosis
ciprofloxacin	Cystitis Pyelonephritis	3 days 7-14 days	?Safety in pregnancy Achilles tendon rupture
gentamicin	Severely ill patients with pyelonephritis, prostatitis		Only IV Nephrotoxic Ototoxic

Table 22. Erectile Dysfunction Medications

Drug	Class	Mechanism	Indication	Adverse Effects
sildenafil (Viagra®) tadalafil (Cialis®) vardenafil (Levitra®)	Phosphodiesterase 5 inhibitor	Selective inhibition of PDE5 (enzyme which degrades cGMP) Leads to sinusoidal smooth muscle relaxation and erection	ED when some erection present	Severe hypotension Contraindicated if Hx of priapism, or in conditions predisposing to priapism (leukemia, myelofibrosis, polycythemia, sickle cell disease) Contraindicated with nitrates
alprostadil (MUSE: Male Urethral Suppository for Erection)	Prostaglandin E ₁	Activation of cAMP, relaxing sinusoidal smooth muscle Local release (capsule inserted into urethra)	ED	Penile pain Presyncope
alprostadil (intracavernosal injection) triple therapy also used: papaverine, phentolamine, PGE ₁	See above	See above	ED	Thickening of tunica albuginea at site of repeated injections (Peyronie's plaque) Painful erection Hematoma Contraindicated if Hx of priapism, or in conditions predisposing to priapism

Table 23. Benign Prostatic Hyperplasia Medications

Drug	Class	Mechanism	Indication	Adverse Effects
terazosin (Hytrin®) doxazosin (Cardura®) tamsulosin (Flomax®) alfuzosin (Xatral®)	Alpha 1 blockers Alpha 1a selective Alpha 1a selective	Alpha-adrenergic antagonists reduce stromal smooth muscle tone Reduce dynamic component of bladder outlet obstruction	BPH	Presyncope Leg edema Retrograde ejaculation Headache Asthenia Nasal congestion
finasteride (Proscar®) dutasteride (Avodart®)	5 alpha-reductase inhibitor	Blocks conversion of testosterone to DHT Reduces static component of bladder outlet obstruction Reduces prostatic volume	BPH	Sexual dysfunction PSA decreases

Note: All alpha-blockers developed for BPH have similar efficacy, however, alpha-1 selective agents have an improved side effect profile.

Table 24. Prostatic Carcinoma Medications

Drug	Class	Mechanism	Indication	Adverse Effects
leuprolide (Lupron®, Eligard®), goserelin (Zoladex®)	GnRH agonist	Initially stimulates LH, increasing testosterone and causing "flare" (clinically: increased bone pain), later causes low testosterone	CaP (N>0, M>0)	Hot flashes Headache Decreased libido
*diethylstilbestrol (DES)	Estrogens	Inhibit LH and cytotoxic effect on tumour cells	As above	Increased risk of cardiovascular events
*cyproterone acetate	Steroidal antiandrogen	Competes with DHT for intracellular receptors: 1. Prevent flare produced by GnRH agonist 2. Use for complete androgen blockade 3. May preserve potency	As above	
flutamide (Eulexin®) bicalutamide (Casodex®)	Non-steroidal antiandrogen	As above	As above	Hepatotoxic: AST/ALT monitoring
*ketoconazole, spironolactone	Steroidogenesis inhibitors	Blocks multiple enzymes in steroid pathway, including adrenal androgens	As above	GI symptoms Hyperkalemia Gynecomastia

*Very rarely used

Table 25. Continence Agents

Drug	Class	Mechanism	Indication	Adverse Effects
oxybutynin (Ditropan®)	Antispasmodic	Inhibits action of ACh on smooth muscle Decreases frequency of uninhibited detrusor contraction Diminishes initial urge to void	Urge incontinence + urgency + frequency	Dry mouth Blurred vision Constipation Supraventricular tachycardia
oxybutynin (Ditropan®) tolterodine (Detrol®) trospium (Trosec®) solifenacin (Vesicare®) darifenacin (Enablex®)	Anticholinergic	Muscarinic receptor antagonist Selective for bladder Increases bladder volume Decreases detrusor pressure	Urge incontinence + urgency + frequency	As above
imipramine	Tricyclic antidepressant	Sympathomimetic effects: urinary sphincter contraction Anticholinergic effects: detrusor relaxation	Stress and urge incontinence	As above Weight gain Orthostatic hypotension Prolonged PR interval

Note: All anti-cholinergics are equally effective and long acting formulations (Detrol LA® and Ditropan XL®) are better tolerated. Newer muscarinic M3 receptor specific agents (solifenacin, darifenacin) are equally efficacious as older drugs, however, RCTs based on head-to-head comparison to long acting formulations are lacking.

References

General Information

American Urological Association. <http://www.auanet.org/guidelines/>
 American Association of Family Physicians. <http://www.aafp.org/afp/20020415/1589.html>
 Ferri F. Practical Guide to the care of the medical patient (6th ed.) 2006. St. Louis: Mosby.
 Goldman L, Ausiello D. Cecil Textbook of Medicine (22nd ed.) 2004. Philadelphia: Saunders (Elsevier).
 Macfarlane MT. House Officer Series: Urology. (3rd ed.) 2001. Philadelphia: Lippincott Williams & Wilkins.
 Tanagho EA, McAninch JW. Smith's General Urology. (16th ed.) 2004. McGraw-Hill Companies, Inc.
 Urology Channel. <http://www.urologychannel.com>
 Wein AJ, Kavoussi LR, Novick AC, Partin AW and C Peters CA. Campbell's Urology. (9th ed.) 2006. Philadelphia: WB Saunders Co.

Common Presenting Problems

Cohen RA and Brown RS. Microscopic hematuria. New England Journal of Medicine. 2003;348:2330-2338
 Morton AR, Iliescu EA and Wilson JWL. Nephrology: 1. Investigation and treatment of recurrent kidney stones. CMAJ 166(2):213-218, Jan 2002
 Teichman JMH. Acute renal colic from ureteral calculus. New England Journal of Medicine. 2004;350:684-693

Urological Emergencies

Galejs LE. Diagnosis and treatment of the acute scrotum. American Family Physician. 1999;59(4):817-24

Medications

Bill-Axelson A, Holmberg L, Ruutu M, et. al. Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer. NEJM. 2005; 352: 1977-84.
 Common Medications: Gray J (Editor). Therapeutic Choices (4th ed). Canadian Pharmacists Association, Ottawa, 2003.
 Micromedex health care series. www.micromedex.com
 Rini B, Halabi S, Rosenberg J, et. al. Bevacizumab Plus Interferon Alfa Compared with Interferon Alfa Monotherapy in Patients with Metastatic Renal Cell Carcinoma: CALGB 90206. J. Clin. Onc. 2008; 26: 5422-28.

Common Unit Conversions

To convert from the conventional unit to the SI unit, **multiply** by conversion factor

To convert from the SI unit to the conventional unit, **divide** by conversion factor

	Conventional Unit	Conversion Factor	SI Unit
ACTH	pg/mL	0.22	pmol/L
Albumin	g/dL	10	g/L
Bilirubin	mg/dL	17.1	μmol/L
Calcium	mg/dL	0.25	mmol/L
Cholesterol	mg/dL	0.0259	mmol/L
Cortisol	μg/dL	27.59	nmol/L
Creatinine	mg/dL	88.4	μmol/L
Creatinine clearance	mL/mon	0.0167	mL/s
Ethanol	mg/dL	0.217	mmol/L
Ferritin	ng/mL	2.247	pmol/L
Glucose	mg/dL	0.0555	mmol/L
HbA1C	%	0.01	proportion of 1.0
Hemaglobin	g/dL	10	g/L
HDL cholesterol	mg/dL	0.0259	mmol/L
Iron, total	μg/dL	0.179	μmol/L
Lactate (lactic acid)	mg/dL	0.111	mmol/L
LDL cholesterol	mg/dL	0.0259	mmol/L
Leukocytes	x 10 ³ cells/mm ³	1	x 10 ⁹ cells/L
Magnesium	mg/dL	0.411	mmol/L
MCV	μm ³	1	fL
Platelets	x 10 ³ cells/mm ³	1	x 10 ⁹ cells/L
Reticulocytes	% of RBCs	0.01	proportion of 1.0
Salicylate	mg/L	0.00724	mmol/L
Testosterone	ng/dL	0.0347	nmol/L
Thyroxine (T ₄)	ng/dL	12.87	pmol/L
Total Iron Binding Capacity	μg/dL	0.179	μmol/L
Triiodothyronine (T ₃)	pg/dL	0.0154	pmol/L
Triglycerides	mg/dL	0.0113	mmol/L
Urea nitrogen	mg/dL	0.357	mmol/L
Uric acid	mg/dL	59.48	μmol/L

Celsius → Fahrenheit $F = (C \times 1.8) + 32$

Fahrenheit → Celsius $C = (F - 32) \times 0.5555$

Kilograms → Pounds 1 kg = 2.2 lbs

Pounds → Ounces 1 lb = 16 oz

Ounces → Grams 1 oz = 28.3 g

Inches → Centimetres 1 in = 2.54 cm

Commonly Measured Laboratory Values

Test	Conventional Units	SI Units
Arterial Blood Gases		
pH	7.35-7.45	7.35-7.45
PcO ₂	35-45 mmHg	4.7-6.0 kPa
PO ₂	80-105 mmHg	10.6-14 kPa
Serum Electrolytes		
Bicarbonate	22-28 mEq/L	22-28 mmol/L
Calcium	8.4-10.2 mg/dL	2.1-2.5 mmol/L
Chloride	95-106 mEq/L	95-106 mmol/L
Magnesium	1.3-2.1 mEq/L	0.65-1.05 mmol/L
Phosphate	2.7-4.5 mg/dL	0.87-1.45 mmol/L
Potassium	3.5-5.0 mEq/L	3.5-5.0 mmol/L
Sodium	136-145 mEq/L	136-145 mmol/L
Serum Nonelectrolytes		
Albumin	3.5-5.0 g/dL	35-50 g/L
ALP	35-100 U/L	35-100 U/L
ALT	8-20 U/L	8-20 U/L
Amylase	25-125 U/L	25-125 U/L
AST	8-20 U/L	8-20 U/L
Bilirubin (direct)	0-0.3 mg/dL	0-5 µmol/L
Bilirubin (total)	0.1-1.0 mg/dL	2-17 µmol/L
BUN	7-18 mg/dL	1.2-3.0 mmol/L
Cholesterol	<200 mg/dL	<5.2 mmol/L
Creatinine (female)	10-70 U/L	10-70 U/L
Creatinine (male)	25-90 U/L	25-90 U/L
Creatine Kinase – MB fraction	0-12 U/L	0-12 U/L
Ferritin (female)	12-150 ng/mL	12-150 µg/L
Ferritin (male)	15-200 ng/mL	15-200 µg/L
Glucose (fasting)	70-110 mg/dL	3.8-6.1 mmol/L
HbA1C	<6%	<0.06
LDH	100-250 U/L	100-250 U/L
Osmolality	275-300 mOsm/kg	275-300 mOsm/kg
Serum Hormones		
ACTH (0800h)	<60 pg/mL	<13.2 pmol/L
Cortisol (0800h)	5-23 µg/dL	138-635 nmol/L
Prolactin	<20 ng/mL	<20 ng/mL
Testosterone (male,free)	9-30 ng/dL	0.31-1 pmol/L
Thyroxine (T ₄)	5-12 ng/dL	64-155 nmol/L
Triiodothyronine (T ₃)	115-190 ng/dL	1.8-2.9 nmol/L
TSH	0.5-5 µU/mL	0.5-5 µU/mL
Hematologic Values		
ESR (female)	0-20 mm/h	0-20 mm/h
ESR (male)	0-15 mm/h	0-15 mm/h
Hemoglobin (female)	12.3-15.7 g/dL	123-157 g/L
Hemoglobin (male)	13.5-17.5 g/dL	140-174 g/L
Hematocrit (female)	36-46%	36-46%
Hematocrit (male)	41-53%	41-53%
INR	1.0-1.1	1.0-1.1
Leukocytes	4.5-11 x 10 ³ cells/mm ³	4.5-11 x 10 ⁹ cells/L
MCV	88-100 µm ³	88-100 fL
Platelets	150-400 x 10 ³ /mm ³	150-400 x 10 ⁹ /L
PT	11-15 s	11-15 s
PTT	25-35 s	25-35 s
Reticulocytes	0.5-1.5% of RBC	20-84 x 10 ⁹ /L

Abbreviations

μmol	micromoles	ACST	asymptomatic carotid surgery trial	ALT	alanine aminotransferase
μE3	unconjugated estriol	ACT	activated clotting time	AM	morning
1,25(OH) ₂ -vit D	1,25-dihydroxy-vitamin D	ACT-D	actinomycin D	AMA	anti-mitochondrial antibodies
111-In DTPA	111-in diethylene triamine	ACTH	adrenocorticotrophic hormone	AMAN	acute motor axonal neuropathy
	penta acetic acid	ACV	assist-control ventilation	AMI	acute myocardial infarction
17-KS	17-ketosteroids	AD	Alzheimer's disease	AMI	acute myocardial ischemia
17-OH prog	17-hydroxyprogesterone	AD	atopic dermatitis	AML	acute myeloid leukemia
18FDG	18-fluorodeoxyglucose	AD	autosomal dominant	AMM	agnogenic myeloid metaplasia
2-PAM	pralidoxime	AD	right ear	AMP	adenosine monophosphate
5-ASA	5-aminosalicylic acid	ADC	apparent diffusion coefficient	AMSAN	acute motor-sensory axonal neuropathy
5-HT	serotonin	ADH	antidiuretic hormone		
		ADHD	attention-deficit/hyperactivity disorder	AN	acoustic neuroma
				AN	anorexia nervosa
		ADL	activities of daily living	ANA	antinuclear antibody
		ADM	abductor digiti minimi	ANC	absolute neutrophil count
		ADME	absorption, distribution, metabolism and elimination	ANCA	anti-neutrophil cytoplasmic antibody
		ADP	abductor pollicis	ANOVA	analysis of variance
		ADP	adenosine diphosphate	ANS	autonomic nervous system
		ADR	adverse drug reaction	Anti-GBM	anti-glomerular basement membrane
		ADRs	adverse drug reactions		
		AE	adverse event	Anti-LKM	anti-liver kidney microsome
		AER	active external rewarming	Anti-Sm	anti-Smith antibodies
		AF	amniotic fluid	AO	aortic root
		AFB	acid-fast bacillus	AOM	acute otitis media
		Afib	atrial fibrillation	AoV	aortic valve
		AFLP	acute fatty liver of pregnancy	AP	anterior-posterior
		AFP	alpha-fetoprotein	APB	atrial premature beat
		AFV	amniotic fluid volume	APB	abductor pollicis brevis
		AG	anion gap	APC	activated protein C
		Ag	antigen	APCKD	adult polycystic kidney disease
		AGA	appropriate for gestational age	APH	antepartum hemorrhage
		AGE	advanced glycosylated end-products	APL	abductor pollicis longus
				APLA	anti phospholipid antibody
		AGUS	atypical glandular cells of undetermined significance	APLAS	anti phospholipid antibody syndrome
		AHA	American Heart Association	APML	acute promyelocytic myeloid leukemia
		AHI	apnea hypopnea index	APo	apolipoprotein
		AHTR	acute hemolytic transfusion reactions	ApoA	apolipoprotein A-1
				ApoB	apolipoprotein B
		AICA	anterior internal carotid artery	APR	abdominal perineal resection
		AICA	anterior inferior cerebellar artery	APS	antiphospholipid antibody syndrome
		AIDP	acute inflammatory demyelinating polyneuropathy	APTT	activated partial thromboplastin time
		AIDS	acquired immune deficiency syndrome	APUD	amine precursor uptake and decarboxylation
		AIHA	autoimmune hemolytic anemia	AR	aortic regurgitation
		AIJ	angiotensin II	AR	attributable risk
		AIN	acute interstitial nephritis	AR	autosomal recessive
		AIN	allergic interstitial nephritis	ARB	angiotensin receptor blocker
		AIN	anterior interosseous nerve	ARBC	anti-ribonuclear protein complex
		AION	acute ischemic optic neuropathy	ARDS	acute respiratory distress syndrome
		AION	arteritic anterior ischemic optic neuropathy		
				ARF	acute renal failure
		AIS	androgen insensitivity syndrome	ARI	absolute risk increase
		AJR	abdominal jugular reflex	ARMD	age-related macular degeneration
		AK	actinic keratosis	ARR	absolute risk reduction
		aka	also known as	ART	advanced reproductive technologies
		AKI	acute kidney injury		
		ALL	acute lymphoblastic leukemia	ART	assisted reproductive technologies
		ALND	axillary lymph node dissection		
		ALP	alkaline phosphatase		
		ALS	amyotrophic lateral sclerosis		

ARV	anti-retroviral	bid	two times a day	CaO ₂	arterial O ₂ content
AS	aortic stenosis	BiPAP	bilevel positive airway pressure	CAP	Canada Assistance Plan
AS	ankylosing spondylitis	BI-RADS®	breast imaging reporting and data system	CAP	community acquired pneumonia
AS	left ear	BK	below knee	CAP	prostatic carcinoma
ASA	above sternal angle	BM	basement membrane	CAS	Children's Aid Society
ASA	acetylsalicylic acid	BM	bowel movement	CAVHD	continuous arterial-venous hemodialysis
ASA	American Society of Anesthesiology	BM	bone marrow	CBC	complete blood count
ASC-H	atypical squamous cells, cannot exclude HSIL	BMD	Becker muscular dystrophy	CBD	common bile duct
ASCUS	atypical squamous cells of undetermined significance	BMD	bone mineral density	CBF	cerebral blood flow
ASD	atrial septal defect	BMI	body mass index	CBGD	cortical basal ganglionic degeneration
ASIL	anal squamous intraepithelial lesion	BMR	basal metabolic rate	CBI	continuous bladder irrigation
ASIS	anterior superior iliac spine	BMT	bone marrow transplant	CBT	cognitive behavioural therapy with meals
ASO	anti-streptolysin O	BN	bulimia nervosa	cc	carotid-cavernous
ASOT	anti-streptolysin O titers	BNP	brain natriuretic peptide	C-C	coracoclavicular ligament
ASPD	antisocial personality disorder	BOOP	bronchiolitis obliterans with organizing pneumonia	CC	chief complaint
AST	aspartate transaminase	BP	blood pressure	CCB	calcium channel blocker
AST	aspartate amino-transferase	BP	bullous pemphigus	CCB	Consent and Capacity Board
AT II	angiotensin	BPD	biparietal diameter	CCHD	congenital cyanotic heart disease
ATLS	advanced trauma life support	BPD	bronchopulmonary dysplasia	CCK	cholecystokinin
ATN	acute tubular necrosis	BPH	borderline personality disorder	CCR	complete cytogenetic response
ATP	adenosine triphosphate	BPH	benign prostatic hyperplasia	CCP	chronic pelvic pain
ATRA	all-trans-retinoic acid	BPP	benign prostatic hypertrophy	CCS	Canadian Cardiovascular Society
AU	each ear	BPPV	biophysical profile	CCT	central corneal thickness
AUA	American Urological Association		benign paroxysmal positional vertigo	CCU	coronary care unit
AUB	abnormal uterine bleeding	BPV	benign positional vertigo	CD	conduct disorder
AV	atrioventricular	BRAO	branch retinal artery occlusion	CD	Crohn's disease
AV	arteriovenous	BRBPR	bright red blood per rectum	CDC	Center for Disease Control
AVA	aortic valve area	BRVO	branch retinal vein occlusion	CDD	childhood disintegrative disorder
AVF	arterio-venous fistula	BS	blood sugar	CDH	congenital dislocation of the hip
AVM	arteriovenous malformation	BSA	body surface area	CDH	congenital dysplasia of the hip
AVN	atrioventricular node	BSE	bovine spongiform encephalopathy	CEA	carcinoembryonic antigen
AVN	avascular necrosis	BSO	bilateral salpingo-oophorectomy	CEA	cost effectiveness analysis
AVNRT	atrioventricular nodal reentrant tachycardia	BSS	balanced salt solution	CEE	conjugated equine estrogen
AVPU	alert, verbal, pain, unresponsive	BT	bleeding time	CER	control group event rate
AVRT	atrioventricular reentrant tachycardia	BTE	behind the ear	CF	counting fingers
AXR	abdominal x-ray	BUN	blood urea nitrogen	CF	cystic fibrosis
AZT	azidothymidine	BUT	break-up time	CFCs	chlorofluorocarbons
		BV	bacterial vaginosis	CFPC	College of Family Physicians of Canada
		BVH	bilateral ventricular hypertrophy	CFS	chronic fatigue syndrome
		BW	body weight	CFTR	cystic fibrosis transmembrane conductance regulator
		BZ	benzodiazepine		colony forming units

B

B ₁₂	vitamin B ₁₂
BAC	bronchioalveolar cancer
BAD	bipolar affective disorder
BAEP	brainstem auditory evoked potentials
BAL	bronchoalveolar lavage
BBB	bundle branch block
BBB	blood-brain barrier
BC	bone conduction
BCC	basal cell carcinoma
BCG	bacille Calmette-Guérin
BCP	birth control pill
BCS	breast conserving surgery
BE	barium enema
BE	Barrett's esophagus
BG	blood glucose
β-hCG	beta-human chorionic gonadotropin
BHL	bilateral hilar lymphadenopathy

C

C&S	culture and sensitivity	CFU	colony forming units
C/S	Caesarean section	CGL	chronic granulocytic leukemia
C/T	cardiothoracic ratio	CGMP	cyclic guanine monophosphate
CA	coracoclavicular ligament	CHA	Canada Health Act
Ca	calcium	CHD	congenital heart disease
CA	cancer	CHF	congestive heart failure
CA-125	cancer antigen 125	CHL	conductive hearing loss
CABG	coronary artery bypass graft	CHO	carbohydrate
CAD	coronary artery disease	C/I	contraindications
CAH	congenital adrenal hyperplasia	CI	cardiac index
Cal/d	calories/day	CI	cervical incompetence
CAM	complementary alternative medicine	CI	confidence interval
cAMP	cyclic adenosine monophosphate	CIC	clean intermittent catheterization
c-ANCA	cytoplasmic antineutrophil cytoplasmic antibody	CIDP	chronic inflammatory demyelinating polyneuropathy
CaO ₂	combined arterial O ₂	CIN	cervical intraepithelial neoplasia
		CIS	carcinoma in situ
		CJD	Creutzfeldt-Jakob disease
		CK	creatine kinase
		CKD	chronic kidney disease
		CK-MB	creatine kinase-MB

CI	cardiac index	CSA	central sleep apnea	DHE	dihydroergotamine
CI	cervical incompetence	CSF	cerebrospinal fluid	DHEA	dihydroepiandrosterone
Cl	chloride	CSM	central steady and maintained	DHEAS	dihydroepiandrosterone sulfate
CI	confidence interval	C-spine	cervical spine	DHP	dihydropyridine
CIWA	Clinical Institute Withdrawal Assessment	CSR	Cheyne-Stokes respiration	DHP-CCB	dihydropyridine calcium channel blocker
CL	clearance	CT	cognitive therapy	DHT	dihydrotestosterone
CL	corpus luteum	CT	computed tomography	DI	diabetes insipidus
CLL	chronic lymphocytic leukemia	CTA	CT angiogram	DIC	disseminated intravascular coagulation
CM	cardiomyopathy	CTD	connective tissue disease	DID	dissociative identity disorder
CMA	Canadian Medical Association	CTEV	congenital talipes equinovarus	DIEP	deep inferior epigastric perforator
CMC	carpo-metacarpal joint	CTG	cardiotocography (fetal)	DIP	distal interphalangeal joint
CME	continuing medical education	CTLA-4	cytotoxic T-lymphocyte associated protein 4	DKA	diabetic ketoacidosis
CMF	cyclophosphamide, methotrexate and 5-fluorouracil	CTO	community treatment order	DM	dermatomyositis
CMG	cystometrogram	CTS	carpal tunnel syndrome	DM	diabetes mellitus
CML	chronic myeloid leukemia	CUP	central venous pressure	DM1	type 1 diabetes
CMPA	Canadian Medical Protective Association	CV	cardiovascular	DM2	type 2 diabetes
CMT	Charcot Marie Tooth Disease	CVA	cerebrovascular accident	DMARD	disease modifying anti-rheumatic drugs
CMV	cytomegalovirus	CVA	costovertebral angle	DMC	dilated cardiomyopathy
CN	cranial nerve	CVD	cardiovascular disease	DMD	Duchenne muscular dystrophy
CN	cyanide	CVD	cerebrovascular disease	DMSA	dimercaptosuccinic acid
CNH	central neurogenic hyperventilation	CVD	collagen vascular disease	DMSO	dimethylsulfamethoxazole
CNS	central nervous system	CVP	central venous pressure	DMT	disease-modifying therapy
CO	carbon monoxide	CVS	chorionic villus sampling	DMY	dermatomyositis
CO	cardiac output	CVS	cardiovascular system	DNA	deoxyribonucleic acid
CO ₂	carbon dioxide	CVVHD	continuous venous venous hemodialysis	DNCB	dinitrochlorobenzene
COMT	catechol-O-methyl transferase	CWP	coal worker's pneumoconiosis	DNET	dsyembryoplastic neuroepithelial tumour
COPD	chronic obstructive pulmonary disease	CXR	chest x-ray	DNR	do not resuscitate
COX	cyclo oxygenase	CYP	cytochrome p-450	DNSI	deep neck space infections
COX-2	cyclo oxygenase-2			DPD	distal phalangeal depth
CP	cerebral palsy			DPG	diphosphoglycerate
CP	chest pain			DPL	diagnostic peritoneal lavage
CPA	cerebellar pontine angle			DR	diabetic retinopathy
CPAP	continuous positive airway pressure			DRD	dopamine responsive dystonia
CPB	cardiopulmonary bypass			DRE	digital rectal exam
CPD	cephalopelvic disproportion			DRUJ	distal radioulnar joint
CPK	creatine phosphokinase			DS	double strength
CPM	central pontine myelinolysis			DS	Down syndrome
CPM	continuous passive motion			DSA	digital subtraction angiography
CPOE	chest pain on exertion			DSD	detrusor-sphincter dyssynergia
CPP	cerebral perfusion pressure			DSM	Diagnostic and Statistical Manual of Mental Disorders
CPP	chronic pelvic pain			DST	dexamethasone suppression test
CPPD	calcium pyrophosphate dihydrate			DT	delirium tremens
CPPS	chronic pelvic pain syndrome			DTaP	diphtheria, tetanus, acellular pertussis
CPR	cardiopulmonary resuscitation			DTPA	diethylene triaminepentacetic acid
CPSO	College of Physicians and Surgeons of Ontario			DTR	deep tendon reflexes
CQI	continuous quality improvement			DU	duodenal ulcer
Cr	creatinine			DUB	dysfunctional uterine bleeding
CRAO	central retinal artery occlusion			DVT	deep vein thrombosis
CRC	colorectal cancer			DWI	diffusion-weighted image
CrCl	creatinine clearance			Dx	diagnosis
CRF	cardiac risk factor			DXM	dexamethasone
CRF	chronic renal failure			DZ	dizygotic
CRH	corticotropin releasing hormone				
CROS	contralateral routing of signals				
CRP	C-reactive protein				
CRPS	complex regional pain syndrome				
CRS	congenital rubella syndrome				
CRVO	central retinal vein occlusion				
CS	completed stroke				

D

D	diopter
D&C	dilatation and curettage
D/T	due to
D5W	5% dextrose in water
DA	dopamine
DALY	disability adjusted life year
DASH	dietary approaches to stop hypertension
dB	decibel
dBp	diastolic blood pressure
D&C	dilatation and curettage
D/C	discontinue
DC	direct current
DCIS	ductal carcinoma in situ
DCM	dilated cardiomyopathy
Dco	diffusing capacity of carbon monoxide
DCR	dacryocystorhinostomy
DCT	distal convoluted tubule
DDAVP	1-desamino-8-d-arginine vasopressin
DDH	developmental dysplasia of hip
DDT	dichlorodiphenyl trichloroethane
DDx	differential diagnosis
DES	diethylstilbestrol
DES	diffuse esophageal spasm
DES	drug eluting stent
DEXA	dual-energy x-ray absorptiometry
DF	dissociative fugue
DFA	direct fluorescent antibody
DH	dermatitis herpetiformis

Toronto Notes 2011

functional endoscopic sinus surgery

FET	forced expired time
FEV ₁	forced expiratory volume in 1 second
FF	filtration fraction
FFA	free fatty acid
FFP	fresh frozen plasma
FHF	fulminant hepatic failure
FHR	fetal heart rate
FHx	family history
FIGO	International Federation of

FiO ₂	fraction of oxygen in inspired air
FISH	fluorescence in situ hybridization
FL	femur length
FLAIR	fluid-attenuated inversion recovery
Flu	influenza
FN	false negative
FNA	fine needle aspiration
FNHTR	febrile nonhemolytic transfusion reactions

FOBT	fecal occult blood test
FOOSH	fall on outstretched hand
FP	false positive
FPB	flexor pollicis brevis
FPG	fasting plasma glucose
FPL	flexor pollicis longus
FRC	functional residual capacity
FRCPC	Fellow of the Royal College of Physicians of Canada
FRCSC	Fellow of the Royal College of Surgeons of Canada
FSGS	focal segmental glomerular

FSH	follicular stimulating hormone
FT4I	free thyroxine index
FTA-ABS	fluorescent treponemal antibody-absorption
FTS	first trimester screen
FTSG	full thickness skin graft
FTT	failure to thrive
FU	fluorouracil
FUO	fever of unknown origin
FVC	forced vital capacity

g	gram(s)
G/U	genitourinary
G6PD	glucose-6-phosphate dehydrogenase
GA	general anesthetic
GA	gestational age
GABA	gamma aminobutyric acid
GABHS	group A β -hemolytic <i>Streptococcus</i>
GAD	generalized anxiety disorder
GAF	global assessment of functioning
GAS	group A β -hemolytic <i>Streptococcus</i>
GAT	goldmann applplanation tonometry
GB	gallbladder
GBM	glioblastoma multiforme
GBM	glomerular basement membrane
GBS	group B <i>Streptococcus</i>

GBS	Guillain-Barré syndrome	HCCA	Health Care Consent Act	HSIL	high grade squamous intraepithelial lesion
GC	<i>Neisseria gonorrhea/gonococcus</i>	hCG	human chorionic gonadotropin	HSP	Henoch-Schönlein Purpura
GCA	giant cell arteritis	HCl	hydrochloric acid	HSV	herpes simplex virus
GCS	Glasgow coma scale	HCM	hypertrophic cardiomyopathy	HT	height
G-CSF	granulocyte – colony stimulating factor	HCO ₃	bicarbonate	HTLV	human T-cell leukemia/lymphoma virus
GCT	glucose challenge test	HCP	hydrocephalus	HTN	hypertension
GDM	gestational diabetes mellitus	Hct	hematocrit	HUS	hemolytic uremic syndrome
GDP	gross domestic product	HCTZ	hydrochlorothiazide	HVA	homovanillic acid
GE	gastroesophageal	HCV	hepatitis C virus	Hx	history
GERD	gastroesophageal reflux disease	HD	heart disease	HZ	herpes zoster
GFR	glomerular filtration rate	HD	Huntington's disease	HZV	herpes zoster virus
GGT	gamma-glutamyltranspeptidase	HDL	high density lipoprotein		
GH	growth hormone	HDL-C	high density lipoprotein cholesterol		
GHB	gamma hydroxybutyrate	HDV	hepatitis D virus		
GHRH	growth hormone-releasing hormone	HE	hypoaque enema		
GI	gastrointestinal	HELLP	hemolysis, elevated liver enzymes, low platelets		
GIFT	gamete intra fallopian transfer	HEV	hepatitis E virus	I	iodide
GIT	gamete-immediate transfer	HF	heart failure	I&D	incision and drainage
GIT	gastrointestinal tract	HHT	hereditary hemorrhagic telangiectasia	I&D	irrigation and debridement
GIST	gastrointestinal stromal tumour	HHV	human herpes virus	IA	intra-arterial
GJ	gastrojejunal	HI	head injury	IABP	intra-aortic balloon pump
GM	germinal matrix	Hib	<i>Haemophilus influenzae</i> b	IADL	instrumental activities of daily living
GMC	general medical condition	HIDA scan	hepatobiliary iminodiacetic acid scan	IBD	inflammatory bowel disease
GM-CSF	granulocyte macrophage – colony stimulating factor	HIDS	Hospital Insurance and Diagnostic Services Act	IBM	inclusion body myositis
GMN	glomerulonephritis	HIE	hypoxic ischemic encephalopathy	IBM	intermenstrual bleeding
GMO	genetically modified organism	HIFU	high intensity focused ultrasound	IBS	irritable bowel syndrome
GN	glomerulonephritis	HIT	heparin induced thrombocytopenia	IBW	ideal body weight
GN	Gram negative	HIV	human immunodeficiency virus	IC	ileocecal
GNB	Gram negative bacilli	HJR	hepatojugular reflex	IC	immune complex
GNG	gluconeogenesis	HL	hearing loss	IC	inspiratory capacity
GNP	gross national product	HLA	human leukocyte antigen	ICD	implantable cardioverter defibrillator
GnRH	gonadotropin-releasing hormone	HLA	human leukocyte antigen	ICD	irritant contact dermatitis
GPC	giant papillary conjunctivitis	HLHS	hypoplastic left heart syndrome	ICF	intracellular fluid
GPe	globus pallidus pars externa	HM	hand motion	ICH	intracerebral hemorrhage
GPi	globus pallidus pars interna	HMD	hyaline membrane disease	ICH	intracranial hemorrhage
GSW	gunshot wound	HMG-CoA	hydroxymethylglutamyl coenzyme A	ICP	intracranial pressure
GT	glucose tolerance	HMO	Health Maintenance Organization	ICS	inhaled corticosteroid
GTN	gestational trophoblastic neoplasia	HMPAO	hexamethylpropene aminooxime	ICSI	intracytoplasmic sperm injection
GTPAL	gravidity, term infants, parity, abortions, living children	HMSN	hereditary motor-sensory neuropathy	ICU	intensive care unit
gtt	drops	HNPCC	hereditary non-polyposis colorectal cancer	ID	identifying data
GU	genito-urinary	HO	heterotopic ossification	ID	internal diameter
GVHD	graft versus host disease	HOCM	hypertrophic obstructive cardiomyopathy	IDL	intermediate density lipoprotein
		HONK	hyperglycemic hyperosmolar non-ketotic coma	IDM	infant of diabetic mother
		HP	hydrostatic pressure	IE	infective endocarditis
h	hour	HPA	human platelet antigen	IEM	inborn errors of metabolism
H	hydrogen	HPA	hypothalamic pituitary adrenal	IF	immunofluorescence
H/A	headache	HPD	histrionic personality disorder	IF	internal fixation
HA	hemagglutinin	HPF	high power field	IF	intrinsic factor
HA	hemolytic anemia	HPI	history of present illness	IFA	immunofluorescence assay
HAART	highly active antiretroviral treatment	HPL	human placenta lactogen	IFG	impaired fasting glucose
HAV	hepatitis A virus	HPO	high frequency oscillation	Ig	immunoglobulin
Hb	hemoglobin	HPS	hepatopulmonary syndrome	IgA	immunoglobulin A
HbA1C	glycosylated hemoglobin	HPV	human papilloma virus	IGF-1	insulin-like growth factor
HBIg	hepatitis B immune globulin	HR	heart rate	IgG	immunoglobulin G
HBsAg	hepatitis B surface antigen	HRCT	high resolution CT scan	IgM	immunoglobulin M
HBV	hepatitis B virus	HRT	hormone replacement therapy	IGT	impaired glucose tolerance
HC	head circumference	HSG	hysterosalpingography	IHD	ischemic heart disease
HCC	hepatocellular carcinoma			IL	interleukins
				IL-1	interleukin-1
				IL-6	interleukin-6
				ILD	interstitial lung disease
				ILR	implantable loop recorder

H

IM	intramedullary				LD ₅₀	lethal dose – 50%
IM	intramuscular			J	L-dopa	levodopa
IMA	inferior mesenteric artery	J	jaeger		LDH	lactate dehydrogenase
IMB	intermenstrual bleeding	JA	juvenile arthritis		LDL	low density lipoprotein
IMF	idiopathic myelofibrosis	JC	Jakob-Creutzfeldt		LDL-C	low density lipoprotein cholesterol
IMF	intermaxillary fixation	JGA	juxtaglomerular apparatus		LE	lower extremities
IMR	infant mortality rate	JIA	juvenile idiopathic arthritis		LEEP	loop electrosurgical excision procedure
IMV	intermittent mandatory ventilation	JNA	juvenile nasopharyngeal angiofibroma		LEMS	Lambert-Eaton myasthenic syndrome
INCS	intranasal corticosteroids	JRA	juvenile rheumatoid arthritis		LES	lower esophageal sphincter
INF	interferon	JVP	jugular venous pulsation		LFT	liver function test
INF- α	interferon- α				LGA	large for gestational age
INH	isoniazid			K	LGI	lower gastrointestinal
INO	internuclear ophthalmoplegia				LH	luteinizing hormone
INR	international normalized ratio				LHF	left heart failure
IO	intraosseous				LHRH	luteinizing hormone releasing hormone
IOC	intra-operative cholangiography	K	potassium		Li	lithium
IOL	induction of labour	KCI	potassium chloride		LICS	left intercostal space
IOL	intraocular lens	kg	kilogram		LIMA	left internal mammary artery
IOP	intraocular pressure	KOH	potassium hydroxide		LITA	left internal thoracic artery
IP	interphalangeal	KRP	Kolmer Reiter protein		LKM	liver kidney microsome
IP	intraperitoneal	KS	Kaposi's sarcoma		LLD	left lateral decubitus
IPAA	ileal pouch-anal anastomosis	KUB	kidney, ureter, bladder		LLDP	left lateral decubitus position
IPAH	idiopathic pulmonary arterial hypertension				LLL	left lower lobe
IPD	interphalangeal depth			L	LLQ	left lower quadrant
IPF	idiopathic pulmonary fibrosis				LLSB	left lower sternal border
IPMN	intraductal papillary mucinous neoplasm	L	litre		LM	light microscope
IPS	integrated prenatal screen	L	live births		LMA	laryngeal mask airway
IPV	injected polio vaccine	L/S	lecithin/sphingomyelin		LMCC	Licentiate of the MCC
IQ	intelligence quotient	LA	left atrium		LMN	lower motor nerve
IR	immediate release	LA	local anesthetic		LMN	lower motor neuron
IRMA	intra retinal microvascular abnormalities	LA	long-acting		LMNL	lower motor neuron lesion
IS	internal sphincter	LABA	long-acting beta-agonist		LMP	last menstrual period
ISA	intrinsic sympathomimetic action	LAC	lupus anticoagulant		LMW	low molecular weight
ISD	intrinsic sphincter deficiency	LAD	left anterior descending		LMWH	low molecular weight heparin
ITE	in the ear	LAD	left axis deviation		LN	lymph node
ITP	immune thrombocytopenic purpura	LAD	lymphadenopathy		LNMP	last normal menstrual period
IU	international units	LAE	left atrial enlargement		LOC	level of consciousness
IUD	intrauterine death	LAFB	left anterior fascicular block		LP	light perception
IUD	intrauterine device	LAH	left atrial hypertrophy		LP	lumbar puncture
IUFD	intrauterine fetal demise	LAP	left atrial pressure		LPFB	left posterior fascicular block
IUGR	intrauterine growth restriction	LAP	leukocyte alkaline phosphatase		LPL	lipoprotein lipase
IUI	intrauterine insemination	LAR	lower abdominal resection		LPS	lipopolysaccharide
IV	intra venous	LAR	lower anterior resection		LR	likelihood ratio
IVC	inferior vena cava	LASIK	laser-assisted in-situ keratomileusis		LRA	leukotriene receptor antagonist
IVDU	intravenous drug use	LBB	left bundle branch		LRTI	lower respiratory tract infection
IVF	in-vitro fertilization	LBBB	left bundle branch block		LSB	left sternal border
IVH	intraventricular hemorrhage	LBD	Lewy body disease		LSC	lichen simplex chronicus
IVIG	intravenous immunoglobulin	LBO	large bowel obstruction		LSD	lysergic acid diethylamide
IVM	in-vitro maturation	LPB	lower back pain		LSIL	low grade squamous intraepithelial lesion
IVP	intravenous pyelogram	LBW	low birth weight		L-T4	L-thyroxine, levothyroxine
IVU	intravenous urography	LCA	left circumflex artery		LTP	laryngotracheoplasty
		LCA	left coronary		LTRA	leukotriene receptor antagonist
		LCAT	lecithin-cholesterol acyltransferase		LUD	left uterine displacement
					LUL	left upper lobe
		LCCN	light chain cast nephropathy		LUQ	left upper quadrant
		LCD	liquor carbonis detergens		LUTS	lower urinary tract symptoms
		LCDC	Laboratory Center for Disease Control		LV	left ventricle
		LCIS	lobular carcinoma in situ		LVAD	left ventricular assist device
		LCL	lateral collateral ligament		LVED	left ventricular end diastolic
		LCx	left circumflex artery		LVEDP	left ventricular end diastolic pressure
		LD	loading dose			

LVEF left ventricular ejection fraction
 LVES left ventricular end systolic
 LVF left ventricular failure
 LVF left ventricular function
 LVFP left ventricle filling pressure
 LVH left ventricular hypertrophy
 LVI lymphovascular space invasion
 LVOT left ventricular outflow tract
 LVP left ventricular pressure

M

M male
 M Muscarinic
 MABP mean arterial blood pressure
 MAC minimum alveolar concentration
 MAC Mycobacterium avium complex
 MAHA microangiopathic hemolytic anemia
 MAI mycobacterium avium-intracellular
 MALT mucosal associated lymphomatous tissue lymphoma
 MAO monoamine oxidase
 MAOI monoamine oxidase inhibitor
 MAOIs monoamine oxidase inhibitors
 MAP magnesium ammonium phosphate
 MAP mean arterial pressure
 MAS meconium aspiration syndrome
 MAST military anti-shock trousers
 MAT multifocal atrial tachycardia
 MC metacarpal
 MCA middle cerebral artery
 MCC Medical Council of Canada
 MCCQE Medical Council of Canada qualifying exam
 MCD minimal change disease
 MCH mean corpuscular hemoglobin
 MCHC mean corpuscular hemoglobin concentration
 MCI mild cognitive impairment
 MCL medial collateral ligament
 MCN mucinous cystic neoplasm
 MCP metacarpal phalangeal joint
 MCT medium chain triglycerides
 MCTD mixed connective tissue disease
 MCV mean corpuscular volume
 MCV molluscum contagiosum virus
 MD maintenance dose
 MD medical doctor
 MD muscular dystrophy
 MDAC multidose activated charcoal
 MDCT multidetector computed tomography
 MDD major depressive disorder
 MDE major depressive episode
 MDI metered dose inhaler
 MDI multiple daily injections
 MDMA 3,4-methylenedioxy-methamphetamine (ecstasy)
 MDR multi-drug resistance
 MDS myelodysplastic syndrome
 MEA microwave endometrial ablation
 MEE middle ear effusion

MEI middle ear inflammation
 MELAS mitochondrial myopathy, encephalopathy, lactic-acidosis and stroke like episodes
 MELD model for end stage liver disease
 MEN multiple endocrine neoplasia
 Men-C meningococcal conjugate vaccine
 MF mycosis fungoides
 mg milligram
 Mg magnesium
 MG myasthenia gravis
 MGUS monoclonal gammopathy of unknown significance
 MH malignant hyperthermia
 MHA Mental Health Act
 MHA-TP microhemagglutination test for Ab to *T. pallidum*
 MHC major histocompatibility complex
 MI myocardial infarction
 MIBG meta-iodo-benzoguanide
 MIDD monoclonal Ig deposition disease
 min minutes
 MLF medial longitudinal fasciculus
 MM malignant melanoma
 MM millimeters
 MM multiple myeloma
 MMF mycophenolate mofetil
 MMFR maximal mid-expiratory flow rate
 MMFR mid maximal flow rate
 MMI methimazole
 MMLE mini-mental status exam
 MMR maternal mortality rate
 MMR measles/mumps/rubella
 MMSE mini mental status examination
 MOA mechanism of action
 MOCA Montreal cognitive assessment
 MODS multiple organ dysfunction syndrome
 MODY maturity-onset diabetes of the young
 MOSF multi-organ system failure
 MP mercaptopurine
 MPA medroxyprogesterone acetate
 MPGN membranous proliferative glomerulonephritis
 MPI myocardial perfusion imaging
 MPTP methylphenyl tetra hydroadipine
 MPV mean platelet volume
 MR mitral regurgitation
 MR magnetic resonance
 MR mental retardation
 MR mitral regurgitation
 MRA magnetic resonance angiogram
 MRC Medical Research Council
 MRCP magnetic resonance cholangiopancreatography
 MRI magnetic resonance imaging
 MRM modified radical mastectomy
 MRN medical record number
 MRSA methicillin-resistant *S. aureus*
 MS mitral stenosis
 MS multiple sclerosis
 MSA mixed sleep apnea
 MSA multiple system atrophy
 MSAFP maternal serum alpha-fetoprotein
 MSDS material safety data sheets

MSE mental status examination
 MSG monosodium glutamate
 MSH melanocyte-stimulating hormone
 MSK musculoskeletal
 MSM men who have sex with men
 MSS maternal serum screen
 MSSA methicillin sensitive *S. aureus*
 MSU mid-stream urine
 MT metatarsal
 MTC medullary thyroid cancer
 MTP metatarso phalangeal joint
 MTX methotrexate
 MTX-FA methotrexate-folinic acid
 MUA manipulation under anesthesia
 MUGA multiple gated acquisition scan
 MUSE male urethral suppository for erection
 MV mitral valve
 MVA mitral valve area
 MVA motor vehicle accident
 MVC motor vehicle collision
 MVO₂ myocardial O₂ consumption
 MVP mitral valve prolapse
 MW molecular weight
 MZ monozygotic

N

N normal
 Na sodium
 N/A not applicable
 N₂O nitrous oxide
 NA neuraminidase
 NA noradrenaline
 NAC n-acetyl
 NAFLD non-alcoholic fatty liver disease
 NAION nonarteritic anterior ischemic optic neuropathy
 NAIT neonatal alloimmune thrombocytopenia
 NASH nonalcoholic steatohepatitis
 NASSA noradrenergic and specific serotonin antagonists
 NATP neonatal alloimmune thrombocytopenia purpura
 NBUVB narrow band ultraviolet B
 NBUVC narrow band ultraviolet C
 NC neurogenic claudication
 NCEP National Cholesterol Education Program
 NCN neocellular nevus
 NCS nerve conduction studies
 NCV nerve conduction velocity
 NDRI norepinephrine and dopamine reuptake inhibitors
 Nd:YAG neodymium-doped yttrium aluminium garnet
 NE norepinephrine
 NEC necrotizing enterocolitis
 NERD non-erosive reflux disease
 NF neurofibromatosis
 NF-1 neurofibromatosis type 1
 NF-2 neurofibromatosis type 2
 NG nasogastric

NG-tube	nasogastric tube
NHL	non-Hodgkin's lymphoma
NHP	natural health product
NICU	neonatal intensive care unit
NIPPV	noninvasive positive pressure ventilation
NIV	noninvasive ventilation
NK	natural killer
NLD	nasolacrimal duct
NLE	neonatal lupus erythematosus
NLP	no light perception
NMDA	N-methyl-D-aspartic acid
NMJ	neuromuscular junction
NMR	neonatal mortality rate
NMS	neuroleptic malignant syndrome
NMSC	nonmelanoma skin cancers
NNH	number needed to harm
NNSGRC	National Newborn Screening and Genetics Resource Center
NNT	number needed to treat
NO	nitric oxide
NOS	not otherwise specified
NP	nasopharyngeal
NPC	nasopharyngeal carcinoma
NPH	normal pressure hydrocephalus
NPO	nothing by mouth, nil per os
NPV	negative predictive value
NREM	non-REM
NRFHR	non-reassuring fetal heart rate
NRT	nicotine replacement therapy
NS	nasogastric tube
NS	nephrotic syndrome
NS	normal saline
NSAIDs	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
NSR	normal sinus rhythm
NST	non-stress test
NSTEMI	non ST elevation myocardial infarction
NT	nuchal translucency
NTD	neural tube defects
NTG	nitroglycerin
NTT	nasotracheal tube
NTUS	nuchal translucency ultrasound
N/V	nausea and vomiting
N/V/D	nausea/vomiting and diarrhea
NVI	neurovascular intact
NVS	neurovascular status
NWB	non-weightbearing
NYD	not yet diagnosed
NYHA	New York Heart Association

O&P	ova and parasites
O/E	on examination
O ₂	oxygen
OA	occiput anterior
OA	osteoarthritis
OAF	osteoclast activating factor
OCD	obsessive compulsive disorder
OCP	oral contraceptive pill
OCPD	obsessive-compulsive personality disorder
OD	oculus dexter
OD	once a day
OD	overdose
OD	right eye
ODB	Ontario Drug Benefit
ODD	oppositional defiant disorder
ODM	opponens digiti minimi
OE	otitis externa
OECD	Organization for Economic Co-operation and Development
OGCT	oral glucose challenge test
OGD	oesophagogastro-duodenoscopy
OGTT	oral glucose tolerance test
OHA	oral hypoglycemic agent
OHIP	Ontario Health Insurance Plan
OHL	oral hairy leukoplakia
OM	otitis media
OME	otitis media with effusion
ONTD	open neural tube defect
OP	occiput posterior
OC	oncotic pressure
OP	opponens pollicis
OPC	oral contraceptive pill
OPCA	olivopontocerebellar atrophy
OPCAB	off-pump coronary artery bypass
OPLL	ossification of posterior longitudinal ligament
OPV	oral polio vaccine
OR	odds ratio
OR	operating room
ORIF	open reduction internal fixation
OS	oculus sinister; left eye
OSA	obstructive sleep apnea
OT	occiput transverse
OT	occupational therapy
OTC	over the counter
OU	oculus uterque
OU	each eye

P	progesterone
P	psoralens
P/E	physical exam
PA	posteroanterior
PA	pulmonary artery
PAB	premature atrial beat
PABA	para-aminobenzoic acid
PAC	premature atrial contraction
PaCO ₂	arterial partial pressure of carbon dioxide
PACs	premature atrial contractions

PACG	primary angle closure glaucoma
PACU	post-anesthetic care unit
PAD	phlegmasia alba dolens
PAG	plasma anion gap
PAH	para-aminohippuric acid
PAHO	Pan American Health Organization
PAI-I	plasminogen activator inhibitor
PAN	polyarteritis nodosa
p-ANCA	perinuclear anti-neutrophil cytoplasmic antibody
PaO ₂	arterial oxygen pressure
PAO ₂	partial pressure of oxygen in alveolar gas
PAP	Papanicolaou
PAP	pulmonary arterial pressure
PAPP-a	pregnancy-associated plasma protein
PAS	periodic acid-schiff reaction
PAS	peripheral anterior synechiae
PASP	pulmonary artery systolic pressure
PAT	paroxysmal atrial tachycardia
Patm	atmospheric pressure
PB	protein bound
PBC	primary biliary cirrhosis
PBD	percutaneous biliary drainage
pc	after meals
PC	peak concentration
PCA	patient controlled analgesia
PCA	posterior cerebral artery
PCB	polychlorinated biphenyls
PCD	phlegmasia cerulea dolens
PCI	percutaneous coronary intervention
PCKD	polycystic kidney disease
PCL	posterior cruciate ligament
PCNSL	primary central nervous system lymphoma
PCO	posterior capsular opacification
PCO ₂	partial pressure of carbon dioxide
PCOD	polycystic ovarian disease
PCOS	polycystic ovarian syndrome
PCP	pneumocystis carinii pneumonia
PCP	phenylcyclidine
PCR	polymerase chain reaction
PCT	porphyria cutanea tarda
PCT	proximal convoluted tubule
PCV	pressure control ventilation
PCWP	pulmonary capillary wedge pressure
PD	Parkinson's disease
PD	personality disorder
PD	posterior descending (artery)
PDA	patent ductus arteriosus
PDD	pervasive developmental disorder
PDE	phosphodiesterase
PDPHA	postdural puncture headache
PDR	proliferative diabetic retinopathy
PE	pulmonary embolism
PEEP	positive end expiratory pressure
PEF	peak expiratory flow
PEI	Prince Edward Island
PER	passive external rewarming
PERLA	pupils equal and reactive to light and accommodation

PET	positron emission tomography scan	PONV	post-operative nausea and vomiting	PUVA	psoralens and long wave ultraviolet radiation
PET	preeclampsia	PPD	post-partum depression	PV	pulmonary valve
PF	patellofemoral joint	PPD	purified protein derivative	PVB	premature ventricular beat
PF	plain films	PPH	postpartum hemorrhage	PVCs	premature ventricular contractions
PFO	patent foramen ovale	PPH	primary pulmonary hypertension	PVD	peripheral vascular disease
PFT	pulmonary function tests	PPHN	persistent pulmonary hypertension of the newborn	PVD	posterior vitreous detachment
PG	plasma glucose	PPI	proton pump inhibitor	PVL	periventricular leukomalacia
PG	prostaglandin	PPRF	paramedian pontine reticular formation	PVR	peripheral venous return
PGE ₁	prostaglandin E ₁	PPROM	preterm premature rupture of membranes	PVR	pulmonary vascular resistance
PGE ₂	prostaglandin E ₂			PYLL	potential years of life lost
Pgp	p-glycoprotein				
PH ₂ O	partial pressure of water	PPS	progressive systemic sclerosis		
PHACES	posterior fossa, hemangioma, arterial anomalies, cardiac, eye	PPV	positive predictive value		
PHE	periodic health examination	PPV	positive pressure ventilation		
PHH	posthemorrhagic hydrocephalus	PR	per rectum	q	each, every
PHIPA	Ontario Personal Health Information Protection Act	PR	progesterone receptor	Q	perfusion
PHPV	persistent hyperplastic primary vitreous	PR	pulmonary regurgitation	QALY	quality adjusted life year
PICA	posterior inferior cerebral artery	PRBCs	packed red blood cells	QD	once a day
PICC	peripherally inserted central catheter	PRK	photorefractive keratectomy	qhs	every night, at bedtime
PID	pelvic inflammatory disease	PRL	prolactin	QID	four times a day
PIE	pulmonary infiltration with eosinophilia	PRN	pro re nata, as needed	QOL	quality of life
PIH	pregnancy-induced hypertension	PROM	premature rupture of membranes	QST	quantitative sensory testing
PIN	posterior interosseous nerve	PRSA	penicillin-resistant <i>S. aureus</i>		
PIP	proximal interphalangeal joint	PRSP	penicillin-resistant <i>Streptococcus pneumoniae</i>		
PIPEDA	Personal Information Protection and Electronic Documents Act	PRUJ	proximal radio ulnar joint	R&M	routine and microscopy
PIV	posterior interventricular artery	PRV	polycythemia rubra vera	R/O	rule out
PK	pyruvate kinase	PS	pulmonary stenosis	RA	rheumatoid arthritis
PKU	phenylketonuria	PSA	progressive supranuclear palsy	RA	right atrium
PL	palmaris longus	PSA	prostate specific antigen	RAAS	renin-angiotensin-aldosterone system
PLT	platelets	Psa	psoriatic arthritis		
PM	evening	PSC	primary sclerosing cholangitis	RAD	right axis deviation
PM	polymyositis	PSD	Parkinson plus syndrome	RAE	right atrial enlargement
PMC	pontine micturition center	PSGN	poststreptococcal glomerulonephritis	RAIU	radioactive iodine uptake
PMDD	premenstrual dysphoric disorder	PSIS	posterior superior iliac spine	RAP	recurrent abdominal pain
PMH	past medical history	PSP	progressive supranuclear palsy	RAP	right atrial pressure
PMI	point of maximal impulse	PSS	progressive systemic sclerosis	RAPD	relative afferent pupillary defect
PML	progressive multifocal leukoencephalopathy	PSSA	penicillin sensitive <i>S. aureus</i>	RAS	renal artery stenosis
PMN	polymorphonuclear neutrophils	PSV	pressure support ventilation	RAS	reticular activating system
PMNs	polymorphonuclear cells	PSVT	paroxysmal supraventricular tachyarrhythmia	RBB	right bundle branch
PMR	proportional mortality rate	PT	physiotherapy	RBBB	right bundle branch block
PMS	premenstrual syndrome	PTA	prothrombin time	RBC	red blood cell
PMY	polymyositis	PTA	percutaneous transluminal angioplasty	RBF	renal blood flow
PND	paroxysmal nocturnal dyspnea	PTC	pure tone audiometry	RCA	right coronary artery
PND	post nasal drip	PTCA	percutaneous transhepatic cholangiography	RCC	renal cell carcinoma
PNET	primitive neuroectodermal tumour	PTCI	percutaneous transluminal coronary angioplasty	RCM	restrictive cardiomyopathy
PNH	paroxysmal nocturnal hemoglobinuria		percutaneous transluminal coronary interventional polytetra fluoroethylene parathyroid hormone	RCPSC	Royal College of Physicians/ Surgeons of Canada
PNS	parasympathetic nervous system	PTFE	PTH-related peptides		
PNS	peripheral nervous system	PTH	preterm labor	RCT	randomized controlled trial
PO	per os, oral, by mouth	PTHrP	post-traumatic stress disorder	RD	retinal detachment
pO ₂	partial pressure of oxygen	PTL	partial thromboplastin time	RDS	respiratory distress syndrome
PO ₄	phosphate	PTSD	propylthiouracil	RDT	rapid antigen detection test
POA	power of attorney	PTT	peptic ulcer disease	RDW	red blood cell distribution width
POAG	primary open angle glaucoma	PTU	pruritic urticarial papules and plaques of pregnancy	ReA	reactive arthritis
POD	post-operative day	PUPPP	posterior urethral valve	REM	rapid eye movement
POD	post obstructive diuresis			RES	reticuloendothelial system
POMC	pro-opiomelanocortin			RIND	reversible ischemic neurological deficit
				RF	radiofrequency
				RF	rheumatoid factor
				RF	risk factor
				RFT	renal function tests

Q

q	each, every
Q	perfusion
QALY	quality adjusted life year
QD	once a day
qhs	every night, at bedtime
QID	four times a day
QOL	quality of life
QST	quantitative sensory testing

R

R&M	routine and microscopy
R/O	rule out
RA	rheumatoid arthritis
RA	right atrium
RAAS	renin-angiotensin-aldosterone system
RAD	right axis deviation
RAE	right atrial enlargement
RAIU	radioactive iodine uptake
RAP	recurrent abdominal pain
RAP	right atrial pressure
RAPD	relative afferent pupillary defect
RAS	renal artery stenosis
RAS	reticular activating system
RBB	right bundle branch
RBBB	right bundle branch block
RBC	red blood cell
RBF	renal blood flow
RCA	right coronary artery
RCC	renal cell carcinoma
RCM	restrictive cardiomyopathy
RCPSC	Royal College of Physicians/ Surgeons of Canada
RCT	randomized controlled trial
RD	retinal detachment
RDS	respiratory distress syndrome
RDT	rapid antigen detection test
RDW	red blood cell distribution width
ReA	reactive arthritis
REM	rapid eye movement
RES	reticuloendothelial system
RIND	reversible ischemic neurological deficit
RF	radiofrequency
RF	rheumatoid factor
RF	risk factor
RFT	renal function tests

Rh	Rhesus				
RHF	right heart failure				
RIA	radio-immune assay	S&S	signs and symptoms	SIADH	syndrome of inappropriate antidiuretic hormone
RICS	right intercostal space	S/E	side effects	SIDS	sudden infant death syndrome
RIMA	reversible inhibitor of MAO-A	SA	semen analysis	SIL	squamous intraepithelial lesion
RIMA	right internal mammary artery	SA	sinoatrial	SIMV	synchronous intermittent mandatory ventilation
RIND	reversible ischemic neurological deficit	SA	sinus arrhythmia	SIRS	systemic inflammatory response syndrome
RITA	right internal thoracic artery	SA	spontaneous abortion	SJS	Stevens-Johnson Syndrome
RL	Ringer's lactate	SABA	short-acting beta-agonist	SL	sublingual
RLL	right lower lobe	SACD	subacute combined degeneration	SLE	systemic lupus erythematosus
RLQ	right lower quadrant	SAH	subarachnoid hemorrhage	SLED	sustained low efficiency dialysis
RLSB	right lateral sternal border	SAN	sinoatrial node	SLP	speech language pathologist
RML	right middle lobe	SaO ₂	hemoglobin oxygen percent saturation	SLR	straight leg raise
RNA	radionucleotide angiography	SARS	severe acute respiratory syndrome	SMA	smooth muscle antibody
RNA	ritonucleic acid			SMA	superior mesenteric artery
RNAO	Registered Nurses' Association of Ontario	SBE	spontaneous bacterial endocarditis	SMV	superior mesenteric vein
RNC	radionuclide cystography	SBO	small bowel obstruction	SMX	sulfamethoxazole
RNI	recommended nutrient intake	SBP	spontaneous bacterial peritonitis	SNB	sentinel node biopsy
ROM	range of motion	sBP	systolic blood pressure	SND	striatonigral degeneration
ROM	rupture of membranes	SC	sternoclavicular	SNHL	sensorineural hearing loss
ROP	retinopathy of prematurity	SC	subcutaneous	SNpc	substantia nigra pars compacta
RP	retinitis pigmentosa	SCA	spinocerebellar ataxia	SNRI	serotonin and norepinephrine reuptake inhibitors
RPE	retinal pigment epithelium	SCA	superior cerebellar artery	SNS	striatonigral degeneration
RPF	renal plasma flow	SCC	squamous cell carcinoma	SNS	sympathetic nervous system
RPGN	rapidly progressive glomerulonephritis	SCD	sickle cell disease	SOB	shortness of breath
		SCD	sudden cardiac death	SOBOE	shortness of breath on exertion
RPR	rapid plasma reagin	SCFA	short chain fatty acids	SOF	superior orbital fissure
RPS	rapid primary survey	SCFE	slipped capital femoral epiphysis	SOGC	Society of Obstetricians and Gynecologists of Canada
RQ	respiratory quotient	SCh	succinylcholine		spreading pigmented actinic keratosis
RR	relative risk	SCI	spinal cord injury	SPAK	
RR	respiratory rate	SCID	severe combined immunodeficiency	SPECT	single photon emission computed tomography
RRR	relative risk reduction				
RRT	renal replacement therapy	SCIWARA	spinal cord injury without radiologic abnormality	SPEP	serum protein electrophoresis
RSD	reflex sympathetic dystrophy			SPF	sun protection factor
RSI	rapid sequence induction	SCLC	small cell lung cancer	SPK	superficial punctate keratitis
RSV	respiratory syncytial virus	SCM	sternocleidomastoid	SR	sinus rhythm
RT	radiation therapy	SCORTEN	severity of illness score for toxic epidermal necrolysis	SRS	stereotactic radiosurgery
rT3	reverse triiodothyronine			SRT	speech reception threshold
RTA	renal tubular acidosis	SCr	serum creatinine	SSA	Sjögren's syndrome A
RTI	respiratory tract infection	ScvO ₂	central venous oxygen saturation	SSB	Sjögren's syndrome B
rt-PA	recombinant tissue plasminogen activator	SD	standard deviation	SSD	Silver Sulphadiazene
		SDAC	single dose activated charcoal	SSPE	subacute sclerosing panencephalitis
RUL	right upper lobe	SDM	substitute decision maker		
RUQ	right upper quadrant	SDRI	selective dopamine re-uptake inhibitor	SSRI	selective serotonin reuptake inhibitor
RV	residual volume			SSS	sick sinus syndrome
RV	right ventricle	SE	status epilepticus	SSSS	staphylococcal scalded skin syndrome
RVAD	right ventricular assist device	SDS	Shy-Drager syndrome		
RVEDP	right ventricular end-diastolic pressure	Seb. K	seborrheic keratosis	STAR	sore throat, arthritis, rash
		SEM	systolic ejection murmur	STDs	sexually transmitted diseases
RVF	right ventricular failure	SEN	subependymal nodules	STEMI	ST elevation myocardial infarction
RVH	right ventricular hypertrophy	SERM	selective estrogen receptor modulator	STfR	soluble transferrin receptor
RVOT	right ventricular outflow tract			STIs	sexually transmitted infections
RVOTO	right ventricular outflow tract obstruction	SERM	selective estrogen receptor modifiers	STN	subthalamic nucleus
				STP	sodium thiopental
RVP	right ventricular pressure	SES	sick euthyroid syndrome	STS	Stevens-Johnson Syndrome
RVSP	right ventricular strain pattern	SES	social economic status	STSG	split thickness skin graft
RVSP	right ventricular systolic pressure	SF	synovial fluid	STSH	sensitive thyroid-stimulating hormone
Rx	treatment	SFH	symphysis fundal height		
		SG	specific gravity	SUI	stress urinary incontinence
		SGA	small for gestational age	SV	stroke volume
		SH	sex hormones	SVI	stroke volume index
		SHBG	sex hormone binding globulin	SVC	superior vena cava
		SHG	sonohysterography		
		SI	sacroiliac		

SVG saphenous vein graft
SVR systemic vascular resistance
SVRI systemic vascular resistance index
SVT supraventricular tachycardia
SWU septic work-up

T

T1 first trimester
T2 second trimester
T3 third trimester
 $t_{1/2}$ half-life
 T_3 triiodothyronine
 T_3 RU T_3 resin uptake
 T_4 thyroxine
TA therapeutic abortion
TAA thoracic aortic aneurysm
TACE transcatheter arterial chemoembolization
TAH total abdominal hysterectomy
TAH/BSO total abdominal hysterectomy + bilateral salpingo-oophorectomy
TB tuberculosis
TBB transbronchial biopsy
TBG thyroid binding globulin
TBI traumatic brain injury
TBSA total body surface area
TBUT tear break up time
TBW total body water
TC total cholesterol
TC transcobalamin
Tc99m-DMSA technetium-99m dimercaptosuccinic acid
Tc99m-DTPA technetium-99m diethylene triamine pentaacetate
Tc99m-ECD technetium-99m ethyl cysteinate dimer
Tc99m-MIBI technetium-99m methoxyisobutyl-isonitrile
TCA trichloroacetic acid
TCA tricyclic antidepressant
TCC transitional cell carcinoma
TCF tracheoesophageal fistula
TCM traditional Chinese medicine
Td tetanus diphtheria – adult type formation vaccine
TD₅₀ toxic dose – 50%
TDEE total daily energy expenditure
TDM therapeutic drug monitoring
TdP tetanus, diphtheria, polio
TE tracheoesophageal
TED thromboembolic disease
TEE transesophageal echocardiography
TEF tracheoesophageal fistula
TEN total enteral nutrition
TEN toxic epidermal necrolysis
TENS transcutaneous electrical neuro stimulation
TET tubal embryo transfer
TFCC triangular fibrocartilage complex

TG triglyceride
TGA transposition of the great arteries
THA total hip arthroplasty
TI therapeutic index
TIA transient ischemic attack
TIBC total iron binding capacity
tid three times a day
TIG tetanus immune globulin
TIN tubulointerstitial nephritis
TIPS transjugular intrahepatic portosystemic shunt
TIVA total intravenous anesthesia
TKA total knee arthroplasty
TKVO to keep vein open
TLC total lung capacity
TLE temporal lobe epilepsy
TM tympanic membrane
TMB transient monocular blindness
TMJ temporomandibular joint
TMP trimethoprim
TMP/SMX trimethoprim-sulfamethoxazole
Tn troponin
TN true negative
TNF tumour necrosis factor
TNF α tumour necrosis factor alpha
TNK tenecteplase
TNM tumour/node/metastasis staging
TOF tetralogy of Fallot
TOF train of four
TORCH toxoplasmosis, rubella, cytomegalovirus, hepatitis
TOT tension-free obturator tape
t-PA tissue plasminogen activator
TP true positive
TP tympanic membrane
TPE tropical pulmonary eosinophilia
TPI treponemal pallidum immobilization
TPN total parenteral nutrition
TPO thyroid peroxidase
TPR total peripheral resistance
TR tricuspid regurgitation
TRALI transfusion related acute lung injury
TRAM transverse rectus abdominis myocutaneous
TRH thyrotropin releasing hormone
TRUS transrectal ultrasound
TS tricuspid stenosis
TSAb thyroid stimulating antibodies
TSH thyroid stimulating hormone
TSI thyroid stimulating immunoglobulin
tsp teaspoon
T-spine thoracic spine
TSS toxic shock syndrome
TT thrombin time
TTB transthoracic biopsy
TTE transthoracic echocardiography
TTG tissue transglutaminase
TTKG transtubular potassium gradient
TTN transient tachypnea of the newborn
TTP thrombotic thrombocytopenic purpura
TUIP transurethral incision of the prostate

TUMT transurethral microwave therapy
TUNA transurethral needle ablation
TURBT transurethral resection of bladder tumour
TURP transurethral resection of the prostate
TV tricuspid valve
TVOT tension-free vaginal obturator tape
TVT tension-free vaginal tape
TVUS trans-vaginal ultrasound
TXA2 thromboxane 2
TZ transformation zone
TZD thiazolidinedione

U

U unit
U/A urinalysis
ud as directed
U/O urine output
U/S ultrasound
UA unstable angina
UAE uterine artery embolization
UC ulcerative colitis
UCL ulnar collateral ligament
UE upper extremity
UES upper esophageal sphincter
UFH unfractionated heparin
UGI upper gastrointestinal
UGIB upper gastrointestinal (GI) bleed
UIP usual interstitial pneumonitis
ULSB upper left sternal border
UMN upper motor nerve
UMN upper motor neuron
UMNL upper motor neuron lesion
ung ointment
Uosm urine osmolality
UPEP urine protein electrophoresis
UPJ ureteropelvic junction
UPPP uvulopalatopharyngoplasty
UPV UV protection factor
URI upper respiratory infection
URTI upper respiratory tract infection
UTI urinary tract infection
UUTS upper urinary tract symptoms
UV ultraviolet
UVA ultraviolet radiation
UVA ultraviolet wavelength A
UVB ultraviolet wavelength B
UVC ultraviolet wavelength C
UVJ ureterovesical junction
UVR ultraviolet radiation

V

V fib	ventricular fibrillation
V	ventilation
VA	ventriculo-arterial
VA	visual acuity
Vd	volume of distribution
VAC	vacuum assisted closure
VADs	ventricular assist devices
Var	Varicella vaccine
VAIN	vaginal intraepithelial neoplasia
VBAC	vaginal birth after Caesarean section
VBI	vertebrobasilar insufficiency
VC	vital capacity
VCUG	voiding cystourethrogram
Vd	volume of distribution
VDRL	venereal disease research laboratory
VFib	ventricular fibrillation
VF	visual field
VHL	von Hippel Lindau syndrome
VIN	vulvar intraepithelial neoplasia
VIP	vasoactive intestinal peptide
Vit. A	vitamin A
VIU	visual internal urethrotomy
VLDL	very low density lipoprotein
VMA	vanillyl mandelic acid
VOR	vestibulo-ocular reflex

VP	vasopressin
VP	ventriculoperitoneal
VPB	ventricular premature beat
VPI	velopharyngeal insufficiency
VPL	ventral posterolateral
VPL	ventral posteromedial
V/Q	ventilation-to-perfusion
VRE	vancomycin-resistant Enterococci
VSD	ventricular septal defect
VSR	vital signs routine
VT	ventricular tachycardia
VT	tidal volume
VTE	venous thromboembolism
VUR	vesicoureteral reflux
VVC	vulvovaginal candidiasis
vWD	von Willebrand's disease
vWF	von Willebrand's factor
VZIG	Varicella-Zoster immunoglobulin
VZV	Varicella-Zoster virus

W

WBC	white blood cell
WBRT	whole brain radiation therapy
WC	waist circumference
WCB	Workers' Compensation Board
WHI	Women's Health Initiative

WHI	Women's Health Institute
WHMIS	Workplace Hazardous Materials Information System
WHO	World Health Organization
WNV	West Nile virus
WPW	Wolff-Parkinson-White
WSIB	Workplace Safety and Insurance Board
WT	weight

X

XRT	radiation therapy
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Z

ZE	Zollinger-Ellison
ZIFT	zygote intrafallopian transfer
ZIFT	zygote-transfer
ZN	Ziehl-Neelsen
ZPP	zinc protoporphyrin

Index

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A

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